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BIOLOGICAL RESEARCH STRATEGY AND PUBLICATION POLICY[1]

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THE difficulties in the field of biological publication, which we are to discuss at this conference, are only partly of a technical and administrative nature and therefore can only partly be overcome by technical and organizational measures. The roots of the problem lie much deeper and concern the whole future of biology.

As publication is merely crystallized research, publication ills are largely an outcome of defective research, and bad research, in turn, may be blamed on bad training for research. The publication problem thus appears as just one aspect of a much broader problem; namely, that of teaching and research in biology in general.

If the volume of publication threatens to surpass what is technically and economically manageable, we must decide on how to meet the threat without hampering scientific progress. Our capacity to process, finance, store and utilize scientific literature is certainly not unlimited. Yet, in the past we have often behaved as if it were. We now realize that we are approaching the critical limit at an ominous pace, and we want to be prepared.

Logically, there are several ways of keeping the volume of publication within reasonable bounds. We might reduce the volume of research production, or we might continue to produce at full capacity but publish only part of it; above all, we might increase the efficiency of both production and publication; that is, the yield, per unit of time, of scientifically useful results, and the yield, per printed page, of scientifically useful statements. In deciding just what course to follow in practice, the long-range interests of biological science as a whole should prevail. However, since biology lacks unity of purpose and has never

[1] Address before the Conference on Publication Problems in Biology, held at the Cleveland meeting of the American Association for the Advancement of Science on September 11, 1944.

developed a deliberate and consistent research policy, we simply do not possess valid criteria by which to judge what would, and what would not, serve the interests of biology as a whole.[2] Our opinions on the subject are diverse and often conflicting, and by their very diversity reveal the part which fashions, local traditions, personal predilection and expediency have played in their molding.

Opinion is too casual and unstable a basis for any science worth its name to rest upon, and if we are really concerned about the future of biological research, the thing to do is to provide it with a firm foundation of principles defining the purpose of research and the methods that have proved most successful in attaining it. The time has come for changing from a drifting to a charted course, not only in the field of publication, but in biological research. This study of the publication problem might, therefore, profitably be made the occasion for initiating a much broader enterprise: a concerted reexamination, reevaluation and restatement of the goals, ways and means of biological research. I shall try to illustrate in the following very sketchy outline how the field of publication would benefit from such a more comprehensive action.

It has become perfectly plain that with the increase of workers flocking into research, the cherished doctrine of freedom for random movements will have to be gradually abandoned. This is not the place to go into a detailed discussion of these matters. All I mean to indicate is that, while the shelling of every new walnut promises to reveal some new configuration on the inside, we shall have to consider how long it is scientifically proficient and economically feasible to continue to shell walnuts in the hope that something worth while will come of it.

There are some basic fallacies current among biological workers. They are: (a) that every as yet unrecorded item is worth recording; (b) that every recorded item is worth reporting; (c) and that every fact worth reporting is worth publishing in print.

There are those who contend—I am sure, quite sincerely—that in science anything at all that has not yet been done is worth doing, and that one fact is as good as any other fact. I respect their viewpoint but can not share it, because it seems to me to be based on an utter misconception of the aim and function of research. It is a perversion of the teachings of the history and philosophy of science to claim that the aim of research is fact finding. The aim of research is knowledge, and as knowledge is not a mere collection of data, research can not consist merely of a compilation of facts. Information does not constitute knowledge. It merely furnishes the food on which knowledge grows. Like food, data must be digested and assimilated before they can be incorporated in the body of knowledge. Like food, they must lose their identity in the process of being assimilated. To expect that a hodge-podge of miscellaneous information is going to sort and order itself automatically into knowledge, is like the illusion of the medieval magician who expected a mixture of chemicals in a retort to organize itself into a homunculus.

Now, if facts are but the food on which knowledge grows, is it not about time that we concern ourselves a little with the dietetics of knowledge to find out which foods are healthy, how they are to be prepared and what constitutes a balanced diet? Certainly, as bulk is no criterion of nutritive value, so the volume of data being piled up can be no measure of the progress of science. The primary aim of research must not be just more facts, but more facts of strategic value.

By strategic value I mean that property of an observation or experiment that leads to the clarification or solution of a problem, to deeper insight into a phenomenon, to the linking of previously unrelated facts and ideas, or simply to the birth of a new problem; at any rate, leads to some end other than the bewildered question, "So, what?"

The crux of the problem, therefore, is to make research workers more strategy-conscious. How? Most of us are vaguely conscious of an unwritten code of scientific strategy, which has been passed down through the medium of example and personal contact from teacher to student. But now that scientific research is assuming mass-production dimensions, this mode of transmission is breaking down. More and more students leave our classrooms for so-called independent research, with barely the faintest notion of what science is all about and of how best to promote it. While they are learning tactical tricks, they rarely come to know those rules of scientific strategy which could give aimfulness to their future research.

Now, if the patriarchal system of instruction, which could give a student perspective, is forced out of operation by sheer pressure of numbers, then we shall have to do what all communities and tribes had to do when they outgrew the patriarchal state in which unwritten convention could pass for law: they had to codify the law, and so we may likewise have to formulate and codify the rules of scientific research. Unless we do, we can not expect an uninitiated generation of to-morrow to observe these rules; for they will not know them.

Yes, I am envisaging a written code of scientific research to serve as a manual of scientific strategy and as a standard frame of reference for the rating of scientific products, for the guidance of research workers, editors and administrators alike. However, in contrast to a code of law, with its powers of

[2] P. Weiss, SCIENCE, 95: 32, 1942.

enforcement, the implementation of this scientific code must be left to the conscience of the research man himself. Conformance must be a matter of his sense of responsibility and judgment, which we, as teachers, must strive to develop, and there must be no coercion. Some will continue to waste their time and somebody's funds on petty tasks, but this will still be much less costly to science than would be any attempt to prescribe certain ways of research and proscribe others. On the other hand, unless we do exercise and teach self-discipline, restraints may be forced upon us from the outside by agencies of much less vision and competence. And this we want to avoid.

The suspicion that I am here advocating a subtle scheme to deprive the scientist of his freedom of decision may be allayed by reiterating that, quite to the contrary, I want us to provide him with a more rational basis on which to make intelligent and responsible decisions. Even now freedom of choice in research is restricted by such factors as pressure of opinion or authority, accidents of training and circumstances, subsidizing policies of institutions and foundations, practical needs, and others. These are extraneous influences. How, then, could any one object to letting biology develop a directive from its own inner resources, namely, the envisaged articles of strategy of scientific research? The quality of both research and publication could only gain from such an educational campaign, which would reduce the aimlessness of thousands of sorcerer's apprentices now busily engaged in swelling the flood of literature. So much for long-range policy.

Of immediate benefit would be the incorporation in our educational program of some instruction to graduate students on how to organize their material for publication. We teach our students to use only clean instruments and glassware, but we do not always insist on similar cleanliness of their mental and verbal tools. We expect them to be meticulous in their observations, manipulations and measurements, but we often let them get away with a muddled presentation of their results. Would it not be wise to develop their sense of proportions and, for instance, call their attention to the fact that they only hurt themselves and irritate the reader by such common practices as camouflaging important results by setting them down in an underbrush of irrelevant trifles?

We must also help the student to steer clear of two extreme and opposite attitudes which he is prone to adopt. On the one hand, there are those who feel that the main thing is to do the work and that publishing it is a side issue. On the other side of the picture, there is the understandable tendency of some to recite for the reader all the little incidents of their research, which have no scientific interest. Adding to this the tendency of "padding" for the mere sake of attaining impressive volume, it can be seen that a lot of improvement might come from proper education at the research end, long before a manuscript reaches the editor.

I have been talking of the student, but the student of to-day is the research worker of to-morrow. If there is nothing we can do about the past, we can at least provide for the future.

Cleanliness of the mental tools and mental operations in the description of scientific results would go a long way in saving publication space. A concrete step in this direction could be made by insisting on more uniform and consistent terminology. If one compares the care with which terminology is treated in physics, and nomenclature in taxonomy, with the terminological carelessness in some other biological fields, the contrast is appalling. Three main improvements could be made with little effort.

(a) The creation of new terms or symbols, even if only for temporary use, to designate complex phenomena or situations, which otherwise would have to be circumscribed at each mention by long-winded phrases, should be encouraged. Authors should acquire the habit of giving a vocabulary of their main terms in the first part of their paper, and then sticking to it.

(b) The creation of new terms for phenomena for which there is already a good old term should be discouraged.

(c) Use of the same term in different meanings by different authors is a common source of controversy, leads to polemics, and should be eliminated.

The time seems ripe for various biological disciplines to attempt some terminological house cleaning, and it might be profitable to encourage the setting up of commissions in each field to attempt a standardization of terms in that field, possibly to be incorporated in sectional dictionaries to which reference could be made whenever the terms are being used in publications.

More serious consideration should be given to the state of digestion at which research results or theories are deemed ready for presentation. This is one of the knottiest problems because it involves so many considerations other than the sheer interest of science; for instance, competition, priority, baiting of funds, institutional publication pressure, etc. This problem reaches over into that of the technique of publication, and the solution may lie in giving factual data which deserve quick diffusion a different treatment from other materials in which the advantage of maturation would outweigh the disadvantage of delay.

One could envisage a bulletin service through which raw research data would be communicated to only those research workers known to be engaged in related work or specifically requesting them. Routed through

a central clearing agency and reproduced mimeographically or by other cheap processes, such bulletins would not only speed the dissemination of information, but would make information available that otherwise would have to remain unreported. Some specialized and highly active branches of biology have already adopted such a scheme unofficially, as it were. There is no reason why it should not be made universal and be given bibliographic recognition. Lack of editorial screening is counterbalanced by the author's awareness of the fact that his information will reach the most critical judges, namely, his peers in the same field.

Relieved thus of the congestion caused by the growing tendency of authors to present their work in installments, publication in print would return to its original function of reporting work which has been brought to some sort of conclusion. Printed publication would be reserved for results and thoughts worthy of more general circulation and of permanent preservation and would no longer dignify the ephemeral.

Let us now turn to some further aspects of the publication problem which would be materially affected by whatever policy biological research would choose to follow.

(1) Biological disciplines have gradually and imperceptibly changed their content and methods so that many of the historical designations which now delimit fields have lost their former meanings. Other fields have not changed in content, but in emphasis. While there has been a tendency to accommodate new trends by establishing new journals, there has been less evidence of re-orientation among the existing ones to adapt themselves to the changes which have occurred. No satisfactory solution of this problem will be reached unless biologists get together and rearrange and reallocate their various disciplines. This could, of course, come only from free, wise and cooperative planning.

(2) Many existing journals are distinguished by their history. It would be deplorable if attempts at standardization and uniformity were driven to the point where individual organs of publication would lose their personal character. However, with all due reverence for historical tradition, certain incongruities of the past are in need of correction. Most serious among these are the duplication of effort and the overlap of domain between journals covering nearly identical fields in a spirit of rivalry. We shall not be able to change the weaknesses of human nature, but we do not have to accord them a prominent place in the determination of our scientific policies.

(3) Institutional administrators, government bureaus, etc., will have to be persuaded that the number of printed pages or articles is no valid measure of a man's productivity and usefulness. That some waste of print can be ascribed to institutional publication pressure is generally recognized. What is not usually pointed out in this connection is that we can not expect administrators to give up the convenience of counter and yardstick as long as many of our scientific societies apply this criterion in ruling on admission to membership. The question of what other criteria to substitute for volume of publication involves the fundamental problem of how to appraise research efforts and assess research achievements, and this again can not be answered otherwise than in terms of certain agreed upon standards of the goals, ways and means of biological research.

(4) Universal adoption of the policy of making publication an integral part of a research project, so that at least part of the publication costs would naturally have to be carried by the institutional, foundational or private funds supporting the research might cure some of the ills. Psychologically, it would make for greater care in publication. Economically, it would discourage expansiveness. Publication is as inseparable and as legitimate a part of research as is the developing of an exposed plate in photography. The objection that funds would thus be deflected that otherwise might be used for productive research is not really serious, for anybody who takes the trouble to look into the concrete figures will soon convince himself that publication costs, by and large, amount to only an insignificant fraction of the total cost of a research project.

In conclusion, our present system of publication in biology, while perhaps capable of temporizing a little longer with the aid of technical improvements, subsidies, stronger editorial control and similar expedients, is admittedly unprepared and unsuited to serve the needs of a science which grows as rapidly and vigorously as biology does. Our collective responsibility for the future of biology forces us to take notice. To take appropriate action will require much wisdom and experience, but above all, vision. It is my plea that whenever such action is taken, the publication problem be dealt with not separately, but as part of the larger problem of biological research, of which it is a natural branch. I feel that education for research, planning of research, prosecution of research, financing of research and publication of research, should each be viewed from the perspective of the whole complex. To be able to do this, we need a more explicit and consistent research policy than we now possess, and it might be a timely undertaking to formulate and codify the unwritten rules of scientific—more particularly, biological—research strategy, for the good of research workers, teachers, students, administrators, legislators, publishers, editors, donors and all others whose actions or inaction may affect the future of our science.

THE ROLE OF NUTRITION IN CANCER PREVENTION[1]

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CANCER represents one of the main causes of death in the United States and is second only to heart disease in this respect. Voegtlin[2] has reported that there are about 500,000 cases of cancer in the United States, with an annual death toll of about 160,000. The incidence of cancer is increasing. During the ten years between 1930 and 1940 the population increased 7 per cent., the number of deaths increased 2 per cent., but the number of deaths from cancer increased 35 per cent. It is difficult to say whether or not this increase in the incidence of cancer is a real increase or whether it is a reflection of increased accuracy in diagnosis, decrease in deaths from other causes or increase in the average age of the population. One doubts whether the accuracy in diagnosis has increased 35 per cent. between 1930 and 1940, and the argument that more people live to be older has little weight because when one considers only the older groups, the incidence of cancer among those who do survive to old age is also increasing. As for the argument of a decrease in deaths from other causes, it should be remembered that the incidence of death due to cancer's chief competitors is also increasing: Every death due to heart disease has the effect of lowering the incidence of cancer, yet both are increasing. Brody,[3] of the University of Missouri, and others, have suggested that the increased incidence of the diseases of old age may be due to the over-nutrition and under-exercise which has accompanied our so-called civilization. The incidence of diabetes among women over 45 was reported to have doubled between 1920 and 1930, and it was shown that between 80 and 90 per cent. of diabetics had been overweight prior to the onset of the disease. There is apparently a correlation between diabetes and cancer, for it has been shown[4] that the incidence of cancer among diabetics is much higher than in the population at large. Furthermore, life insurance records have shown[5] that people who were overweight at the time insurance was taken out were more liable to cancer in later life. I do not need to remind this group that our way of life has changed greatly in the last forty years. You have seen the change with your own eyes. But as a concrete illustration which "dates" the change, let me remind you that between 1910 and 1920 this country changed from the horse-and-buggy stage to the automotive era. That decade occurred during the youth of many people who are now cancer patients. However, I wish to emphasize that we do not draw our conclusions from statistics on human cases but insist on controlled experiments with animals. It is interesting to find that when animals are placed under certain conditions analogous to those of "civilized" man, the incidence of cancer increases, as I shall show later.

One of the questions most frequently asked of cancer investigators is whether the cancer problem is amenable to research, that is, can it be solved, or is it a hopeless task? The answer of course depends upon what is meant by a solution, but I may say that we are confident of ultimate success. There have been many successes in the past, chief of which have been the development of x-ray and radium treatments and emphasis on early diagnosis. More recently, one of our colleagues, Dr. F. E. Mohs, has developed an amazingly successful technique of controlled chemosurgery for the removal of surface cancers. Surgery has also been making steady progress through the years. Nevertheless, I suspect that the public does not regard any of these methods as cures, since they are all amputative in nature, and we are all impressed by the miracles achieved in other fields with the sulfonamides, penicillin, etc. It is clear that the public conception of a cancer cure is very definite, namely, a chemotherapeutic agent for cancer, and even when one from time to time and a recent report on penicillin suggested a selective action on tumor cells *in vitro*. Nevertheless, there is at present no clinically proved chemotherapeutic agent. There are reports of success is developed it may act on only one kind of cancer. For my part I have deliberately turned my back on the search for chemotherapeutic agents, and in the present talk I wish to emphasize cancer prevention. I believe I can show that there is considerable justification for optimism regarding this approach.

CHEMOTHERAPY VS. PREVENTION

There are, then two possible solutions to the cancer problem. One is chemotherapy, and the other is prevention. Most other diseases can be looked upon in a similiar light. As a general proposition, prevention is always preferable to cure, but the public is much more impressed with Dr. Ehrlich's "magic bullet" than they are by the hard and simple facts of syphilis prevention. Perhaps if no chemotherapy were available

[1] Address given at the annual meeting of the South Dakota Academy of Sciences, May 5, 1944, Brookings, S. D.

[2] C. Voegtlin, *Proc. Inst. Med. Chicago*, 14: 16, 1943.

[3] S. Brody, *Ann. Rev. Biochem.*, 4: 383, 1935.

[4] F. Ellinger and H. Landsman, *N. Y. State Jour. Med.*, 44: 259, 1944.

[5] A. Tannenbaum, *Arch. Path.*, 30: 509, 1940.

the demand for quarantining syphilis cases would be as forceful as the demand for quarantining cases of scarlet fever and other contagious diseases for which no chemotherapy is available. In the case of malaria, the importance of quinine and atabrine is undeniable, yet those who are in the field tell us that the most important factor in lowering the malaria toll is prevention. Naturally it must be conceded that a cure which would be as effective for cancer as penicillin is for certain types of infections would be a great blessing to mankind. But if, as I suspect, the answer to the degenerative diseases such as cancer lies in prevention through appropriate self-discipline, then it is possible that under such a program mankind would reap even greater benefits. Without impugning the motives of those who choose the chemotherapeutic approach in research, it can be said that the profit motive alone will guarantee that the search for chemotherapy will continue, and it is appropriate that the cost of this research be carried by the commercial organizations that are most likely to profit from it. On the other hand, we who carry on in State institutions at public expense are in a real sense obligated to carry through the type of research which has no profit motive. For, make no mistake, there will be no reward for a program of cancer prevention. We can not hope to sell it, and in fact I expect we will have difficulty in giving it away.

There are other reasons why we place our emphasis on cancer prevention. In the field of chemotherapy the testing of all possibilities in terms of varying dosage, varying chemicals and varying combinations of chemicals would be an infinite and uninspiring task, in which negative results are virtually worthless. Meanwhile the discovery could easily come as the result of a lucky accident. Some lone research worker could easily stumble upon a chemical or combination of chemicals that would be effective. On the other hand, no one will ever stumble upon the factors involved in cancer prevention; an organized drive, sustained over a period of years, is necessary. A cancer institute is capable of such sustained effort; the lone worker is not. A cancer institute can not afford to use stumbling as an experimental method; the lone research worker, who is earning his livelihood by teaching or practising medicine, can. In my opinion, cancer prevention is more likely to succeed in the long run than is the search for chemotherapy, but in addition I wish to point out that in gaining an understanding of the cancer problem we may be led to a rational method of searching for a chemotherapeutic agent. Furthermore, in gaining an understanding of the fundamental nature of cancer we are getting at the nature of life itself, and the solution to many diseases which are now obscure will be hastened by the results of the studies on the fundamental aspects of the cancer problem.

Experimental Cancer Production

Let us now look at the tools at our disposal. The most important fact is that we can produce cancer in experimental animals at will; we can predict the per cent. which will develop cancer, and we can produce cancer by a variety of methods and in a variety of animals. We are sure that we are dealing with cancers which are comparable in every way with human cancers. But it has taken just about forty years to reach the present position. Cancer was first successfully transmitted from one animal to another in 1898 and 1900, and the first production of a virus tumor was effected about 1908. It was not until 1915 that it was shown that successive applications of tar would produce skin cancer, and it took a further fifteen years for the isolation of a specific carcinogenic (cancer-producing) chemical from the tar. About this time the production of skin cancer by ultraviolet light was discovered accidentally. In 1935 mammary tumors were produced by means of estrin injection and at about the same time the Japanese produced liver tumors by feeding certain azo compounds in the diet. Only in the last two or three years has this technique been standardized sufficiently to be strictly reproducible with diets of known composition. Thus by 1940 we had at our disposal an excellent array of experimental cancer-producing techniques.

The Stages of Cancer Development

Various investigators have begun to realize that the development of a cancer is not confined to the grossly visible events, but that there are a series of imperceptible changes which precede the actual eruption of a malignant cancer. We prefer to divide these events into 3 stages, as follows:

I. *Induction Period:* Result of radiations, chemical carcinogens, heredity, viruses;
II. *Critical Period:* Affected by irritation, injury, caloric intake, exercise;
III. *Period of Progression:* Result of release from restraint of normal cells.

Now, of these three phases, the first is well standardized from an experimental standpoint and is easily controlled. In human cancer, the induction may be caused by excessive radiation including ultra-violet, and in certain cases by extraneous chemical carcinogens, but in most cases it is probably a result of a hereditary defect. However, the mere production of cancer cells as a result of heredity or as a result of painting with a carcinogen does not guarantee that a tumor will result, as can be easily proved. During

the second or critical period the cancer cells are susceptible to environmental changes, and they may regress or they may continue to develop until they suddenly break away from the restraint of the host cells and a malignant cancer suddenly appears.

The Critical Period

The effect of the extrinsic factors could not be studied adequately until the methods for inducing cancer had been worked out, and this has been very recent. My colleague, Dr. H. P. Rusch, recently reviewed[6] the role of the extrinsic factors in cancer production, and it is interesting to note that over 50 per cent. of the 222 papers reviewed had been published between 1939 and 1942. It has been shown by various workers that a restriction of the caloric intake cuts down cancer incidence (see review by Rusch[6]). In one of Tannenbaum's experiments with mice which showed a high incidence of spontaneous (*i.e.*, hereditary) mammary tumors, restriction of the food intake to a maintenance level reduced the cancer incidence from 67 per cent. to zero per cent. There were 50 mice in each group and the experiment was continued for 86 weeks.

The production of tumors by ultra-violet light has been studied intensively by Dr. Rusch and coworkers, who have kindly allowed me to use some of their data. They used 4 groups of 48 young adult mice per group. The effect of a restricted food intake upon longevity, etc., has not always been carried out in a rigorously controlled fashion, and some nutritionists have concluded that the restriction is so severe as to make life (from the human standpoint) so undesirable as to cancel any advantages to be gained by increasing the life span. The experiments by Rusch *et al.* were admirably controlled from a number of standpoints; all four groups received exactly the same amount of protein, salts and vitamins. Two groups received high carbohydrate; the groups were furthermore arranged so that two groups received only sufficient calories to maintain their body weight. They were not emaciated or unhealthy, but they were constantly active, always searching for food; these were the low-calorie animals and received 6.4 calories of food per day. The other two groups are called the high-calorie animals; they received 9.6 calories per day, which is 50 per cent. more than is required to maintain weight. It is just slightly less than they would eat if fed *ad libitum*. The mice received a standard minimal dose of cancer-producing ultraviolet light for 30 minutes every other day. For five months, no cancers appeared. Then, in the high-calorie groups, skin cancers began to appear on the ears. Now, at nine months, none of the high-calorie: high-carbohydrate mice remain. Six of the 48 had died from unknown causes and 42, or 88 per cent., had developed cancer. Among the low-calorie: high-carbohydrate mice, only one, which is 2 per cent., has developed cancer at nine months. The high fat groups showed a similar but less striking calorie effect.

The low-calorie mice receive a great deal of exercise, since they are constantly in motion, whereas the high-calorie mice receive almost no exercise and are quite indolent. In a forced exercise experiment Dr. Rusch also showed a decreased cancer development. The exercised mice ate *less* than the controls and it is thus difficult to say how much of the calorie effect is due to exercise and how much of the exercise effect is due to calories. The calorie effects obviously are not responsible for cancer induction and therefore do not act during the first period. Tannenbaum concluded that the calorie intake did not alter the growth rate of the tumors which did develop. It is evident that the calorie effect acts during the second phase of tumor development, that is, the critical period.

The Effect of Irritation During the Critical Period

The evidence for a critical period also depends on a number of experiments which involve various kinds of irritation. One of the most effective chemical irritants is croton resin, which is a constituent of croton oil. Berenblum painted mice with the carcinogenic hydrocarbon benzpyrene once a week for six months, using a subcarcinogenic concentration of 0.05 per cent. benzpyrene in acetone. Comparable groups were given similar treatment but were painted with dilute solutions of croton oil or croton resin in addition. Benzpyrene or croton oil alone was ineffective, but together they produced cancer. It was also possible to treat mice with a carcinogen for several months, completing the induction period; if the animals were then treated for several months with croton oil during the critical period, cancer resulted. If the croton oil was not applied, the critical period was passed without further development, and regression was the result. As a matter of fact the length of the critical period can be determined, because there comes a time when the application of croton oil will no longer produce cancer following treatment with a carcinogenic hydrocarbon.

Clinicians have frequently associated cancer with burns, yet many people are burned without cancer resulting. What is the relationship here? Again experiments on animals provide the answer:[6] If potential cancer cells are present, a burn can make the difference between a progressing cancer and a regressing cancer. It was shown that with a critical dose of methylcholanthrene for three months, subsequent ap-

[6] H. P. Rusch, *Physiol. Rev.*, 24: 177, 1944.

plications of a small wad of cotton which had been dipped in hot water greatly increased the cancer incidence. The burns alone never produced cancer.

There has also been the question of the relation of physical injury to cancer. Kline and Rusch have shown that a small cut applied twice a month to an area which is in the critical period following tumor induction by methylcholanthrene will cause the development of cancers, while injury alone did not produce cancer.

It is thus apparent that various types of injury, when occurring in the vicinity of potential cancer cells, are capable of completing the sequence of events which culminate in cancer. It is also easy to see how many or most cancers can be associated with injuries, while millions of injuries can occur without producing cancer. The cocarcinogenic effect of irritation and injury upon potential cancers may be expected to occur more or less independently of the plane of nutrition of the host, and the beneficial effect of cancer-preventing nutritional measures during the critical period would therefore be greatest in the absence of chronic irritations.

Restraint by Normal Tissue

It was suggested earlier in this discussion that during the critical period, the cancer cells are susceptible to the influence of the host and are restrained by the normal cells. The basis for this is the fact that the normal sequel to an injury is growth which reaches a certain level and then stops when the injury has been repaired. This growth must stop by some self-regulatory process which is possessed by normal cells but is not possessed by tumor cells. The suppression of tumor growth by normal cells during the critical period undoubtedly occurs through the operation of the mechanism by which normal cells suppress their own growth when this is desirable. The attempt to explain this phenomenon brings us to the role of enzymes and their relation to life, which is the subject of my own researches.

During the forty years between 1900 and 1940, while the tools of cancer research were being forged, a parallel development was occurring in the enzyme field. This development began in 1897 when Büchner produced a cell-free enzyme preparation from yeast and showed that it was capable of fermenting sugar to form alcohol, thereby disproving Pasteur's idea that life was necessary for the fermentation process. The role of phosphate in biological energy transformations was introduced by the Russian Iwanoff and made certain by Harden and Young in England in 1905, when they isolated hexosediphosphate from fermenting extracts. A series of brilliant discoveries, mainly by European workers, followed, and culminated in Warburg's important finding in 1939, in which it was shown that oxidative phosphorylation was the link between fermentation and respiration on the one hand, and life on the other. These many findings I have organized into one chart[7] which shows our present state of knowledge in this field. The true meaning of this slide is shown in a much simpler chart[8] in which we indicate that life is really a community of enzymes which uses part of its food for fuel and part of it for building blocks with which to construct more living matter. In these schemes the word "energy" is essentially synonymous with a particular phosphorylated compound known as adenosinetriphosphate. When a cell is stimulated, this compound is split, and energy is available for function. In addition the split products set in motion a sequence of metabolic events which are designed to restore the original energy reservoir; one of these responses is growth. The relationships were presented in a recent review[7] in which we attempted to show the various responses which may follow a stimulus. The first response is the break-down of ATP to give energy which can be used either for function or for heat. The products of the reaction are adenylic acid and inorganic phosphate, which set in motion the adaptive mechanisms which restore the ATP. The first response is glycolysis. Glycogen breaks down to lactic acid in the presence of phosphate and adenylic acid, and the glycolytic process converts the adenylic acid and inorganic phosphate back to ATP. If the stimulus is stronger and continues longer, the pharmacologic control is called in. This acts both locally, giving vasodilatation, and centrally, giving sympathetic and parasympathetic nervous discharges which result in the secretion of adrenalin, insulin and in other reactions which make increased glycolysis and respiration possible. If the stimulus is severe enough to tax the ability of the organism to resynthesize adenylic and inorganic phosphate to ATP, a compensatory growth will occur, and we believe that this growth is controlled by the fact that these products are important building blocks in the construction of protoplasm, including more enzymes for glycolysis and respiration. When, by the acceleration of metabolism, the animal is able to keep up with the stimulus, the concentration of the building blocks is so low as to prevent growth. Thus growth as well as glycolysis and the pharmacologic mechanisms appear to be organized through this one common denominator. In addition to the responses noted, it appears that in the face of an overwhelming imbalance, the organism goes into a state of shock and dies.

[7] V. R. Potter, "Advances in Enzymology," 4: 201, 1944.

[8] *Ibid.*, *Jour. Am. Diet. Asn.*, 19: 488, 1943.

If we accept for the moment these mechanisms of controlling metabolism and growth, which we shall consider normal, the further step of evolving a cancer theory is obvious. We have proposed that cancer is due to an abnormal protein which is similar to a normal aerobic enzyme protein except that it lacks the catalytic power of the normal enzyme. This abnormal protein could occur accidentally as a result of poor heredity, or it could be produced experimentally by the action of carcinogenic agents on the normal enzymes. Cocarcinogenic agents, injuries and irritations could act by breaking down ATP. Ordinarily this process would simply stimulate the control mechanisms, repair would take place, and the process would stop. However, in the presence of the cancer protein, the process would be sidetracked and there would be no way for the normal cessation of growth to occur.

The nature of the calorie effect and the exercise effect involves the metabolic response which is mediated by the pharmacologic control. It appears to be due to the increased efficiency of the trained animal in working at a lower concentration of fuel and building blocks than can be tolerated by the cancer. In other words, the trained organism can compete with the cancer during the critical period. In the absence of exercise and in a flood of nutrient there is no competition and the cancer thrives. Eventually the cancer passes the critical point and is able to damage the surrounding tissue (possibly by acid) and thereby provide itself with a border of normal cells which behave as if they were treated with a cocarcinogen. The cancer then grows until the host is killed.

In conclusion I wish to re-emphasize that the cancer problem is susceptible to experimental study and that the nature of cancer now seems fairly clear. Animal experiments provide us with a definite guide toward the prevention of cancer in humans. The answer may consist in eating no more than we need and in keeping physically fit, with the addition of proper medical care so that any chronic irritations are eliminated. These precautions demand a considerable degree of self-discipline, but I am confident that as soon as the points are thoroughly established, educational campaigns can get the message across to the people. It is here merely suggested that nutritionists, dietitians, physicians and the public remain as alert to scientific developments regarding the effect of diet restriction and the effect of exercise upon nutritional requirements as they are to developments in dietary adjuvants. The restriction of the quantity of food eaten requires that the quality of the food be carefully controlled. The metabolic studies have other implications, which involve the frequency of food ingestion. The practice of feeding workers six times per day may be sound psychology, but it does not increase the efficiency of their metabolism.[9] It is now clear[10] that the human body adapts itself to various difficult situations by improving its metabolic efficiency. Since maximal metabolic efficiency appears to be related to decreased degenerative disease, the human race is confronted with a nice problem as to how to improve our external environment without weakening our internal environment. We believe that the future of mankind rests on the physical and psychological results inherent in the solution of this problem.

OBITUARY

RECENT DEATHS

DR. ROBERT TUTTLE MORRIS, professor emeritus of surgery of the Post-Graduate Medical School of Columbia University, died on January 9 in his eighty-seventh year.

DR. OSCAR V. BRUMLEY, since 1929 dean of the College of Veterinary Medicine of the Ohio State University, died on January 13 in his sixty-eighth year.

DAVID LUMSDEN, since 1922 and until his retirement in 1941 horticulturist of the Bureau of Entomology and Plant Industry of the U. S. Department of Agriculture, died on January 22 in his seventy-fourth year.

DR. WILLIAM T. ROOT, since 1935 dean of the Graduate School of the University of Pittsburgh, previously head of the department of educational psychology, died on January 24. He was sixty-two years old.

DR. LYDIARD H. W. HORTON, consulting psychologist, Boston, and lecturer on biopsychology at the School of Medicine of Boston University, died on January 19 at the age of sixty-five years.

WILLIAM T. DAVIS, entomologist, president of the Staten Island Institute of Arts and Sciences until his retirement with the title emeritus in 1934, died on January 22 at the age of eighty-two years.

HARRY PHILLIPS TREVITHICK, chief chemist of the New York Produce Exchange, died on January 17 in his fifty-ninth year.

DR. HENRY GREENWOOD BUGBEE, urologist of New York City, died on January 18 in his sixty-fourth year.

PROFESSOR PIERRE ALLORGE, specialist in mosses

[9] See "Symposium on Physiological Fitness," *Fed. Proc.*, 2: 164, 1943.

[10] *Ibid.*, pp. 144, 158.

and algae, a member of the staff of the Laboratoire de Cryptogamie of the Museum d'Histoire Naturelle, Paris, in 1937 president of the Société botanique de France, died on January 21.

VLADIMIR IVANOVICH VERNADSKY, professor of crystallography and mineralogy at the University of Moscow, died on January 6 at the age of eighty-two years.

SCIENTIFIC EVENTS

THE TYPHUS COMMISSION OF THE UNITED STATES OF AMERICA

BRIGADIER GENERAL S. BAYNE-JONES, U.S.A., deputy chief of the Preventive Medicine Service of the Office of the Surgeon General, U. S. Army, and director of the U. S. A. Typhus Commission, has made the following statement:

In the President's Executive Order No. 9285 dated December 24, 1942, establishing the United States of America Typhus Commission, provision is made for research on typhus fever and for collaboration with all appropriate agencies. Ever since the commission went into action in January, 1943, research on typhus fever and the related rickettsial diseases has been one of the main objectives. This research has been conducted in this country and overseas by Typhus Commission personnel, and by investigators in the laboratories of the Army Medical School, the Army Medical Museum, the National Institute of Health, the U. S. Public Health Service and the Naval Medical Research Institute. Furthermore, there has been full collaboration with numerous civilian institutions both in this country and abroad. The work has advanced the understanding of typhus, has improved control measures of both epidemic typhus and scrub typhus and may be leading to the discovery of effective remedies for several types of typhus fever. There are many unsolved problems, but definite progress is being made. The point which I wish to emphasize is that the operation of the U. S. A. Typhus Commission again exemplifies collaboration and coordination of activities of both military and civilian agencies and the drawing to the support of a research program great resources and competent investigators from both military and civilian establishments.

THE WAR AND ENGINEERING EDUCATION

To conserve certain advantages the war has brought, the Carnegie Foundation is conducting a study of measurement and guidance in engineering education at eleven cooperating higher institutions. The undertaking is sponsored jointly by the Engineers' Council for Professional Development, the Society for the Promotion of Engineering Education and the Carnegie Foundation, funds being provided by the two engineering bodies and the Carnegie Corporation of New York.

Based on an inventory of the ability and skills which the entering student of engineering is expected to possess, seven special tests are used to appraise his ability and to assist in assigning and guiding him in his training and choice of career.

Among engineers and educators associated with the work are Robert E. Doherty, B. R. Teare and J. B. Rosenbach, of the Carnegie Institute of Technology; Everett S. Lee and A. R. Stevenson, of the General Electric Company; Alan R. Cullimore and A. D. Moore, of the Newark College of Engineering; R. L. Sackett, of the American Society of Mechanical Engineers; R. H. Frazier and T. P. Pitre, of the Massachusetts Institute of Technology; H. S. Rogers, of the Polytechnic Institute of Brooklyn; Francis M. Dawson and John M. Russ, of the State University of Iowa; T. W. Wood, of Northwestern University, and Carl J. Eckhardt, Jr., of the University of Texas.

ADDITIONAL GRANTS OF THE SUGAR RESEARCH FOUNDATION

FUTURE uses for sugar and new evidence to establish the functions of sugar in the human diet are the object of research now being conducted by college and university investigators under grants-in-aid from the Sugar Research Foundation of New York City.

Founded under the laws of the State of New York on June 10, 1943, the Sugar Research Foundation, of which Joseph F. Abbott is director, is an organization of growers and processors of cane and beet sugar in the continental United States, Hawaii, Puerto Rico, Cuba and Canada. Ody H. Lamborn is the executive director. Dr. Robert C. Hockett, who has leave of absence for five years from the Massachusetts Institute of Technology, where he is associate professor of organic chemistry, is the scientific director.

The purpose of the foundation is to collect and discover facts about sugar—its physiological functions, its chemical characteristics—and to develop its many potential uses.

The first of the grants-in-aid was made to the Massachusetts Institute of Technology, where, in December, 1943, the Sugar Research Foundation Laboratories, a training center for carbohydrate chemists, were established. Here pure and applied organic chemical research on sugars is in progress. This is a five-year project for which the amount appropriated was $125,000.

In addition to the individual grants listed in SCIENCE for January 12 the following grants are reported:

Professor Ancel Keys, laboratory of physiological hygiene, University of Minnesota, for studies of the human requirement for B vitamins.

Professor Julian D. Boyd, department of pediatrics, University Hospital, State University of Iowa, for studies on the arrest by dietary control of dental caries in children.

Professor A. Leroy Johnson and F. J. Stare, Schools of Dental Medicine, Medicine and Public Health, Harvard University, to aid a comprehensive investigation of the etiology and control of dental caries.

Professor Melville L. Wolfrom, department of chemistry, The Ohio State University, for a study of the non-sugar constituents of molasses.

Professor Carl Neuberg, department of chemistry, Washington Square College, New York University, for studies of dry invertase preparations and glycerol production by modified fermentations.

AWARD OF THE ROEBLING MEDAL OF THE MINERALOGICAL SOCIETY OF AMERICA

AT a special luncheon meeting of the Mineralogical Society of America to be held at noon at the Hotel Pennsylvania in New York City, on Tuesday, February 20, the Roebling Medal of the Mineralogical Society of America will be awarded to Professor Edward H. Kraus, dean of the College of Literature, Science and Arts at the University of Michigan. This award is in recognition of meritorious achievements in the fields of crystallography and mineralogy. The meeting will also commemorate the twenty-fifth anniversary of the founding of the society.

Dean Kraus received his B.S. degree from Syracuse University in 1896 and his Ph.D. from the University of Munich, Germany, in 1901. He was called to the University of Michigan in 1904 to take charge of the instruction in crystallography and mineralogy. In addition to his professorship he has held many important executive university positions. Since 1933 he has served as dean of the college. He has published more than seventy-five scientific papers and is sole author of two and co-author of three texts on crystallography, general mineralogy, gems and gem materials and tables for the determination of minerals.

In November, 1944, he was appointed by the Research Club of the University of Michigan to the Henry Russel Lectureship for 1945 for his outstanding work in his special fields of interest.

This will be the fifth award of the Roebling Medal. The four previous recipients were Professor Charles Palache, of Harvard University; Dr. Waldemar T. Schaller, of the U. S. Geological Survey; Dr. Leonard J. Spencer, of the British Museum, and Professor Esper S. Larsen, of Harvard University.

SCIENTIFIC NOTES AND NEWS

THE American Institute of Electrical Engineers gave on January 23 a dinner in honor of Dr. Ernst F. W. Alexanderson, of the General Electric Company, at which he was presented with the Edison Medal, awarded annually by the institute for achievements in the field of electricity, in recognition of his "outstanding inventions and developments in the radio, transportation, marine and power fields."

THE newly established Proctor Gold Medal Award of the Philadelphia Drug Exchange was presented at its eighty-fourth anniversary dinner in Philadelphia on January 23 to Dr. Ivor Griffith, president of the Philadelphia College of Pharmacy and Science, for his "distinguished service in the pharmaceutical field."

DR. E. O. ESSIG, professor of entomology at the University of California at Berkeley, has been awarded a bronze medal by the American Iris Society in recognition of his work in iris hybridization.

THOSE receiving Awards of Merit of the Alumni Society of the University of Pennsylvania include Colonel I. S. Ravdin, Harrison professor of surgery, who holds the Legion of Merit for outstanding services as commander of an Army hospital in India which was organized by the university, and Colonel William S. Middleton, professor of medicine and dean of the Medical School of the University of Wisconsin, who supervises all activities in internal medicine for the American forces in Europe.

DR. R. C. GIBBS, professor of physics at Cornell University, was elected president of the American Association of Physics Teachers at the recent New York meeting held in conjunction with the American Physical Society. The Oersted Medal, awarded annually "for notable contributions to the teaching of physics," was presented to Dr. Homer L. Dodge, president of Norwich University, Vermont. At this meeting Professor I. I. Rabi, of Columbia University, delivered the Richtmyer Memorial Lecture.

CHARLES H. COLVIN, engineering and management consultant of New York City, has been elected president of the Institute of the Aeronautical Sciences. He succeeds Major R. H. Fleet, of San Diego, Calif.

DR. JEAN BROADHURST, professor emeritus of bacteriology of Teachers College, Columbia University, has been elected an honorary member of the New York City Branch of the Society of American Bacteriologists.

AT the School of Medicine of the University of Minnesota, Dr. Gaylord W. Anderson, professor and head of the department of preventive medicine and

public health, who has leave of absence as lieutenant colonel, Medical Corps, Army of the United States, and as chief of the Division of Medical Intelligence of the Office of the Surgeon General, has been named director of the new School of Public Health. Dr. Haven Emerson, of New York, has returned to the school as visiting professor of public health to serve for the year 1945.

DR. CLARENCE H. GRAHAM, professor of psychology at Brown University, has been appointed professor of psychology at Columbia University to take effect in September. He will be in charge of graduate work in experimental psychology.

AT the Ohio University, Dr. J. R. Gentry, Dr. Gaige B. Paulsen and Dr. T. C. Scott have been promoted to full professorships of psychology.

DR. HAROLD M. SELL, associate chemist of the U. S. Field Laboratory for Tung Investigations at Gainesville, Fla., has been appointed research professor in agricultural chemistry at Michigan State College.

DR. JOHN W. GRUNER, of the department of geology of the University of Minnesota, has discovered a new manganese mineral in Minnesota iron ore deposits. The mineral is of a simple composition containing only manganese, hydrogen and oxygen. It has been named Groutite in honor of Dr. Frank E. Grout, head of the Geological Survey of Minnesota.

AT the annual meeting on January 16 of the Anthropological Society of Washington, the following officers were elected: *President,* Dr. T. D. Stewart, U. S. National Museum; *Vice-president,* Dr. Regina Flannery, Catholic University of America; *Secretary,* Dr. William N. Fenton, Bureau of American Ethnology, Smithsonian Institution; *Treasurer,* Dr. Waldo R. Wedel, U. S. National Museum. *Members of the Board of Managers:* Dr. W. M. Cobb, Howard University; Dr. William H. Gilbert, Library of Congress; Dr. Alfred Metraux, Smithsonian Institution; Dr. Maurice A. Mook, American University, and Dr. Julian H. Steward, Smithsonian Institution. Dr. T. D. Stewart was nominated as vice-president to represent the society in the Washington Academy of Sciences.

THE officers of the Association of Official Seed Analysts for the coming year are: *President,* N. G. Lewis, Calgary, Alberta; *Vice-president,* G. P. Steinbauer, Orono, Me.; *Secretary-Treasurer,* Elva Norris, Manhattan, Kans.

DR. R. P. ANDERSON, technologist of the Refining Division of the American Petroleum Institute, has retired from active service.

DR. WALLACE J. ECKERT, astronomer and since 1940 director of the Nautical Almanac Office at the United States Naval Observatory at Washington, D. C., previously professor of astronomy at Columbia University, has been appointed director of the department of pure science recently organized by the International Business Machines Corporation. His office will be at the World Headquarters Building of the corporation in New York City.

DR. WILLARD H. BENNETT, research and development officer for the Signal Corps, has been appointed director of applied research at the Institute of Textile Technology in Charlottesville, Va. He will be responsible for physical and mechanical research and its applications to textile manufacturing operations.

THE *Journal* of the American Medical Association reports that a new cancer research project is planned at the School of Medicine of Western Reserve University to investigate the curative properties of a serum evolved by Dr. Alexander A. Bogomolets, director of the Institute of Experimental Biology and Pathology in the Soviet Union. The work will be carried out under the direction of Dr. Harry Goldblatt, associate director of the Institute of Pathology at the school, who with Dr. Enrique E. Ecker, professor of immunology, has been interested in the serum.

DR. C. L. LUNDELL, director of the Institute of Technology and Plant Industry of the Southern Methodist University at Dallas, has been engaged since 1940 in the preparation of a comprehensive Flora of Texas. With the cooperation of collaborators, four parts of the descriptive flora have been published. A post-graduate research fellowship in systematic botany has now been established. The fellows will conduct research on the flora of the state and will participate in the survey of natural plant resources of the Southwest.

AT the Ohio State University, the annual series of Bownocker lectures, sponsored by the department of geology and the Society of the Sigma Xi, was delivered on January 15 and 16 by Max W. Ball, geologist and petroleum engineer, now of the Petroleum Administration for War. Mr. Ball delivered three addresses entitled "The Search for Oil," "The Athabaska Oil Sands" and "An Adventure in Statecraft." The last was an account of the achievements of the oil industry in cooperation with the Government in providing petroleum products for the war. On January 17 he spoke before the staff of Battelle Memorial Institute on "Fueling the War" and on January 29 gave a broadcast by transcription over radio station WOSU entitled "The Vital Munition."

JOHN E. BARKLEY, who recently resigned as research chemist with the Tennesseee Valley Authority, has become an associate chemist at the Armour Research Foundation, Chicago.

DR. GEORGE WELLS BEADLE, professor of biology at Stanford University, will deliver the fifth Harvey Society Lecture of the current series at the New York Academy of Medicine on February 15. He will speak on "The Genetic Control of Biochemical Reactions."

COLONEL HOWARD A. RUSK, chief of the Convalescent Training Division, Office of the Air Surgeon, Washington, D. C., was expected to deliver on February 12 at the Midwest Conference on Rehabilitation at the Drake Hotel, Chicago, the sixth Frank Billings Lecture of the Thomas Lewis Gilmer Foundation of the Institute of Medicine of Chicago. He had planned to speak on "Rehabilitation—The Challenge to American Medicine." At the request of the War Committee on Conventions, Washington, D. C., however, the conference has been cancelled.

DR. R. RUGGLES GATES gave an address on January 16 at the annual meeting of the New England Ophthalmological Society. His subject was "The Inheritance of Ocular Abnormalities."

A PRELIMINARY Conference on the Problems of Science Teaching in Southern Colleges with representatives from a number of southern institutions in attendance was held at the University of Georgia on January 12 and 13. The University of Georgia has been asked by the Work Conference of the Southern Association of Colleges and Secondary Schools to sponsor a study of instruction in the natural sciences in southern institutions, and the General Education Board has provided funds for the support of certain aspects of this study. This conference was called for the purpose of evaluating work which had been carried out by a local committee and for giving further direction to the study. A later conference, with representatives from all parts of the South, will be held at some subsequent date for the purpose of reviewing reports and recommendations and preparing a final report to the Southern Association of Colleges.

A CONFERENCE on the clinical significance of R_h factors will be held at the Medical Branch at Galveston of the University of Texas on Friday and Saturday, February 9 and 10. It has been called at the suggestion of laboratory workers and Texas military hospitals and will be under the general direction of Dr. J. G. Sinclair, professor of anatomy, and Dr. Henry H. Sweets, director of the John Sealy Clinical Laboratories.

FOLLOWING action by the Corporation of the Polytechnic Institute of Brooklyn providing for the establishment of a Highpolymer Research Bureau, a separate division of polymer chemistry has been established under the direction of Dr. Herman F. Mark, professor of organic chemistry.

THE first specialized course in the reporting and editing of science and medicine for newspapers and magazines will be given at New York University during the academic year 1945–46.

THE *Bulletin* of the U. S. Army Medical Department reports that the Surgeon General has appointed a committee to study and make recommendations concerning the Medical Department in the postwar Army. The chairman of the committee is the chief of the Operations Service, and the recorder is the director of the Special Planning Division. The committee is empowered to call for suggestions on any one connected with the Medical Department. Various subcommittees have been appointed and are already working. Consideration is being given to organization, training, medical supplies and equipment (including research and development), and personnel plans to ensure the highest type of professional medical services to the Army. Specialization will be encouraged and may include specialization in non-professional but related military medical subjects, such as command function in the field with troops, staff work, administration and medical supply duties.

DIRECTORS of the Cooperative Grange League Federation Exchange have appropriated $200,000 for the erection of a building for the School of Nutrition at Cornell University of which Dr. L. A. Maynard is director. This school was established in 1942 and has been sharing the buildings and facilities of other schools. Half the grant becomes available on call of the university and the other half will become available within four years.

THE quarterly *Alumni Bulletin* of the University of Chicago reports that the university plans to establish in the near future a Food Research Institute. In this connection an anonymous gift of $250,000 for botanical work, under the direction of Professor E. J. Kraus, chairman of the department of botany, has been made.

THE John and Mary R. Markle Foundation has made a grant of $3,300 for the support of the studies on filariasis of Dr. J. Allen Scott, associate professor of epidemiology and preventive medicine at the Medical Branch at Galveston of the University of Texas, and a grant of $2,500 for the work on blood flow and hypertension by Dr. Eric Ogden, professor of physiology.

CHEMICALS wanted by the National Registry of

Rare Chemicals of Armour Research Foundation, Chicago, are sodium alpha naphthalene sulfonchloramide, 3-p′-tolueneazo-p-cresol, 3-m′-tolueneazo-p-cresol, 2,3,4- or 2,3,5-trimethyl pyrrole, thorium iodide, o- or p-tolylhydrazine hydrochloride, 2,2,3,3-tetramethyl butane, triphenyl aluminum or antimony, triethyl antimony, tin or thallium, tetraethyl or tetrabutyl tin, d-arabo ascorbic acid, arachidonic acid, allyl cyanamide, 1-allyl piperidine, boroethane, 1-benzyl piperidine or morpholine, bilobol, coenzyme II, 5,6-cyclopenteno-1,2-benzanthracene, and masurium or its compounds.

DISCUSSION

PIGMENT AND BIOCHROME

MY colleague, Professor Fox, has dragged into the open a feud which has been smoldering between us for many years.[1] While the mores of our species, both as to the use of words, and the use of pigments themselves, are little influenced by arguments, it has seemed to me worth while to put some of my contentions in this field on record again.

I have long been irked by some of the prevailing uses, in biology, of the word "pigment." Dr. Fox admits the force of these objections, in part, though he insists upon retaining this word as a convenient vernacular (?) term. For more accurate scientific usage, he has adopted the suggestion of a professor of Greek, and substituted a new word "biochrome."

Whether it is reasonable to set up, as a special class, all the colored substances which can be extracted from animals or plants, in contrast with those substances which do not happen to be colored, is decidedly debatable. However, if we grant the desirability of such a term, "biochrome" would seem to meet the requirements pretty well. That "pigment" does not do so, I have already argued.[2] For this word has a definitely functional connotation, which we can hardly escape. In the inorganic world, colored substances are "pigments" only in so far as they are used as such. Thus lead chromate is (or may be) a pigment; copper sulfate never is. Save for an unfortunate precedent, I can see no excuse for applying any different criterion in the organic world. Why every colored substance, derivable in any way from a living organism, should forthwith become a "pigment" is difficult to understand.

Needless to say, I am offering no general protest against the use of the word "pigment" in biology. I have used the word freely, in connection with my own studies and shall continue to do so. But I believe that the word, when transferred to the organic world, should retain its functional significance. There is no propriety in calling a substance a "pigment" except in so far as it is used by the organism to influence its color scheme. I trust that it is no longer necessary to insist that the *appearance* of an animal is at times one of its important biological assets. Thus, melanin, the carotenoids, guanine and some other substances, occasionally even hemoglobin, may play the functional role of pigments. In so saying, let us repeat, we are not thereby assigning these substances to a definite physical and chemical category.

My chief protest against current usage in this field relates to the expression "respiratory pigment." We are here combining words belonging to two utterly different vocabularies. It is like talking about a "locomotor enzyme" or an "invertebrate catalyzer"! Dr. Fox, in his recent communication to SCIENCE, has given some theoretical reasons for believing that the same features of molecular organization which give to certain substances their color may likewise render them available as oxygen carriers. But even if this association between these attributes should prove to be true, we should hardly be justified in such a bit of semantic miscegenation as we have in "respiratory pigment"! Nor would "respiratory biochrome" be much better.

F. B. SUMNER

SCRIPPS INSTITUTION
OF OCEANOGRAPHY,
LA JOLLA, CALIF.

[1] SCIENCE, November 24, 1944.

[2] *Scientific Monthly*, April, 1937.

LATENT VIRUSES IN STONE FRUITS[1]

RESEARCH workers in the field of stone-fruit viruses have become aware of the presence of latent or hidden viruses or virus complexes in cherry trees. These viruses have been demonstrated by placing apparently healthy sweet or sour cherry buds in various peach varieties, in which case the inoculated peach tree becomes dwarfed, rosetted, with split or cracked bark, ring spots in the foliage or various combinations of the above symptoms. Some trees recover after the initial shock, while others die, apparently depending on the strain or variety of virus present. The more severe strains are easily detected on peach, but the mild strains may cause only a slight dwarfing, with rapid recovery, or may show only an occasional leaf with ring spotting. The Kwanzan and Shirofugen

[1] Published as Technical Paper No. 446 with the approval of the director of the Oregon Agricultural Experiment Station. Contribution from the Botany Department.

varieties of *Prunus serrulata* are proving to be much more reliable test plants for these viruses. When sweet or sour cherry buds having the latent virus complex as it occurs in Oregon are budded into these flowering cherries, a severe reaction occurs.

Kwanzan budded in August with sweet cherry buds containing virus, instead of producing normal growth the following spring, develops small curled leaves with split necrotic veins, which form tight rosettes with very little or no stem elongation. Small nursery trees may be killed, or may produce new growth only below the point of bud insertion. Often the sweet-cherry bud grows and develops in a normal manner and may be the only living branch on the trunk.

Buds from the same source placed into Shirofugen produce an entirely different reaction. If the buds are inserted in August, the area immediately around the bud becomes necrotic and the bud and budding rubber become embedded in a mass of black gum by fall. By spring the stem is completely girdled for 5 or 6 inches, but the foliage and new growth develop in the normal manner. About the time the first leaves have expanded to full size, entire spurs of foliage near the canker suddenly turn brown and die with the leaves still attached. This may gradually spread up one side of the branch or may move on all sides of the branch. As soon as the weather becomes warmer and drier, the entire branch beyond the point of bud insertion suddenly dies. Many of the branches now break over at the point of bud insertion, because this area has become much constricted. The necrosis spreads slowly down from the point of bud insertion and out into the laterals, causing cracking, constrictions and gumming, especially on the new or current-season lateral branches.

When Shirofugen is budded after growth starts in the spring, a similar reaction takes place. Necrosis occurs about the bud insertion and eventually girdles the stem. By fall the canker extends 2 or 3 inches each way from the point of bud insertion, but no symptoms appear on the foliage, until suddenly the entire branch dies. The stem is constricted below the canker, and gum is forced out in tendrils over the necrotic area.

Buds have been taken from several different trees of Bing, Lambert, Royal Ann, Black Republican, Black Tartarian and Montmorency sour cherry and placed on Kwanzan and Shirofugen. Of all the trees tested, only one tree of Bing and one tree of Black Tartarian have failed to give a positive test on these two flowering cherries. Preliminary tests with these two sweet cherry trees have also given negative tests for virus on Elberta peach and Mahaleb seedling. A much more extensive test is now under way to determine if these two trees are free from all known virus.

It is hoped that by testing enough trees one virus-free tree of each of the standard commercial varieties may be found that will serve as a foundation for future nursery stock.

There is some indication that some peach varieties may also carry a somewhat different latent virus that produces a local canker effect on Shirofugen.

A more complete paper on the above subject is being prepared.

J. A. MILBRATH
S. M. ZELLER
OREGON STATE COLLEGE

PENICILLIN SODIUM TREATMENT OF EXPERIMENTAL TRYPANOSOMIASIS OF MICE

THE following preliminary report offers the results of the experiences carried out in order to test sodium penicillin[1] against *Trypanosoma cruzi*.

Two groups of six mice each, weighing about 25 grams each one, were inoculated 33 and 16 days prior to the treatment with the same strain of *Trypanosoma cruzi* kept in our institute by successive passages through dogs.

The total individual dose administered was of 250,000 and 500,000 Oxford units per kilogram to 4 mice of each group. The infection in the 2 untreated mice served as control. The calculated individual dose of sodium salt of penicillin in 0.1 or 0.2 cc of saline solution was given intramuscularly five times daily at 3-hour intervals and twice at night with a 6-hour interval. The entire therapy covered a period of 84 hours.

Parasite observations were made 24 hours after the initial dose and every two days afterwards, for 10 days. The results of the therapy were negatives; both the treated and the untreated mice showed practically the same amounts of trypanosomes in the blood during the treatment and thereafter.

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A NEW QUARRY FOR JURASSIC DINOSAURS

A LARGE deposit of well-preserved dinosaur bones, heretofore undescribed, occurs in the Morrison formation, about 8 miles east of Cleveland, Emery County, Utah. The date and circumstances of original discovery are unknown, but the first systematic investigations were carried out by parties of University of Utah students, who obtained much excellent material. In 1938 the writer brought this deposit to the attention of Dr. G. L. Jepsen, professor of vertebrate

[1] The sodium penicillin was kindly supplied by Winthrop Products, Inc., through the courtesy of Laboratorios Winthrop Ltda., Chile.

paleontology at Princeton University. Grants from the W. B. Scott Research Fund supported a project of excavating and collecting at the site in the summer seasons of 1939, 1940 and 1941. Mr. Malcolm Lloyd, Jr., of Philadelphia, contributed generous aid in 1940 and 1941 and the site has been named the Malcolm Lloyd Jr. Quarry in appreciation of this support. Excavation and packing of the bones was done by the writer, assisted by his brother, L. G. Stokes, and by Don A. Hansen.

The deposit lies in the middle part of the variegated Brushy Basin member of the Morrison formation and bones are exposed for about 225 feet at the edge and surface of a low bench. The rocks dip about 3° northwestward and the overburden becomes increasingly thick in that direction. Over an area of approximately 200 by 75 feet the bone layer can be reached by ordinary open-cut methods. The fossils occur in a layer of marly clay about 2 or 3 feet in thickness and are intermingled with calcareous nodules and concretions. Although a few of the bones have the proper relationship to each other most of them lie in a disarticulated mass.

Partial remains of 19 individual dinosaurs were recovered from excavations which measure in plan about 35 by 25 feet. The specimens are referred to species within the following genera: *Diplodocus. Brontosaurus, Stegosaurus, Camptosaurus, Ceratosaurus* and *Antrodemus*. In addition, bones of a crocodile and teeth of an unidentified reptile were found. Most of the material which was collected has been cleaned and prepared but can not be studied adequately at this time. However, some of the general problems presented and partly investigated may be briefly noted.

Several theories are suggested by the physical characteristics of the Lloyd quarry, which may account for the accumulation of bones at that place. The characteristics of the enclosing sediments and the condition of the bones suggest that the dinosaurs died on the bed of an evaporating pond or lake and that the remains of animals already dead were trampled and disarranged by other dinosaurs in scavenging activities or in efforts to reach the last shallow pools of water. Overlying the bone bed is a 3- to 4-foot layer of almost pure bentonite containing fragments of zircon, quartz, plagioclase, mica and hematite. This material suggests a heavy fall of volcanic ash which could choke and absorb streams of water, overwhelm vegetation and cause widespread destruction. Volcanic activity may have contributed to the death of the dinosaurs at the site of the Lloyd quarry.

The siliceous nature of the bentonitic matrix in which the dinosaur bones were buried is probably responsible for their excellent preservation. Dinosaurs were perhaps no more numerous in Morrison time than in other parts of the Mesozoic, but burial in sediments favorable for petrification has provided a more complete record of this particular time than exists for any other part of the Jurassic.

Carnivorous dinosaurs outnumber the herbivorous types more than two to one in this deposit. In nearly all the other large Morrison bone beds the ratio is reversed and carnivores are rare. The unusually large proportion of carnivorous dinosaurs in the Lloyd quarry may be explained by the scavenging habits of *Antrodemus*. These carnivores may have congregated and perished from hunger among the bones of the herbivores.

This pit furnishes for the first time a fairly complete series of growth stages for a saurischian type of dinosaur. Regardless of whether *Antrodemus* was viviparous or oviparous little has been known of the early growth and development of individual animals. In the Lloyd quarry parts of 10 or 11 specimens of *Antrodemus* were found; these include individuals ranging from about 3 feet high and 6 feet long to 10 feet high and 25 feet long.

Many well-preserved jaws of *Antrodemus* containing full sets of teeth still in place were found and these have yielded new information on the manner of tooth growth and replacement. Although the potential number of teeth was evidently very high, replacements were not haphazard but took place in a definite order. Each tooth in use had next to it on each side either a young tooth coming into use or an old tooth about to be shed. *Antrodemus* was theoretically never left with a gap of more than one tooth's space on each maxillary or dentary bone at any one time, and each gap was flanked by fully functioning teeth of the next series. This process was continuous; excavations in the jaws have revealed three sets of teeth in addition to the two sets in use.

No so-called gastroliths were found with the dinosaur remains of the Lloyd quarry. This lack can not be attributed to the absence of particular kinds of dinosaurs, since all major types are represented. In beds about 200 feet higher there are numerous "gastroliths" but few bones. This evidence suggests that the highly polished siliceous stones so common in the Morrison have no relation to the digestive habits of dinosaurs. In the opinion of some observers the stones achieved their high polish by being exposed for long periods to wind-blown dust. There are, however, many peculiarities of distribution that are hard to explain by any theory except that the stones may have been picked up and carried around by animals.

A composite skeleton of *Antrodemus* composed of bones from several individuals from the Lloyd quarry is ready for mounting and installation after the war

in the Natural History Museum of Princeton University.

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THE "SCIENCE" TALENT SEARCH

THE "Science" Talent Search is in its fourth year. As a teacher of science (and a worker in plant pathology), the writer has regularly brought it to the attention of all science students, has complied with the rules of the contest and has sent the papers of the contestants to the examination committee. During these years, the writer has shared with others the feeling that this may not be a science talent search.

The implications for science teaching of this venture of Westinghouse is such that the methods which are being used, and the conclusions which are being derived, deserve the careful examination of every scientist and of every teacher of science.

Some thought has been given the matter.[1, 2, 3, 4, 5] One fact remains outstanding. The sponsors of the examination persist in calling this a "Science Talent Search" and are apparently heralding this far and wide in what appears to the writer to be a remarkable amount of advertising, in spite of the fact that no one yet knows (within the bounds of scientific method and scientific certainty) just what science talent is.

The sponsors of the examination have an excellent opportunity to gain for science a quantity of data which may determine just what makes a scientist. Assumptions have been made that if a student passes the complete examination (consisting of written examination, essay, interview and review of record) to the satisfaction of the examiners, he has science talent. As a matter of fact, by calling the contest "Science Talent Search," the sponsors seem to have accepted this assumption as a conclusion.

Is this conclusion valid?

Is it possible that students who can not succeed in the written examination and who were successful in the other parts, if given the publicity and opportunities afforded the winners, might make equally good scientists? Is it possible that students who are not among those who "pass" the written examination and who have poor "personalities" (as recorded by teachers), but who have a marked ability to work in high-school science, as shown by an actual undertaking of such work, might still become successful scientists, especially if they obtained the publicity and opportunities afforded the winner?

It is hoped that the sponsors of the Science Talent Search will not neglect the fine opportunity available to them to organize an investigation along experimental lines to determine the nature of science talent. The present Science Talent Search could well be called "Scholarships for Good Students with Present Interests in Science." It is, of course, entirely possible that all that is necessary to be a good scientist is to be a good student with an interest in science. Much would be accomplished if this could be proved scientifically.

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SCIENTIFIC BOOKS

BESSEL FUNCTIONS

A Treatise on the Theory of Bessel Functions. By G. N. WATSON. Second edition. vi + 804 pp. $7\frac{1}{2} \times 10$ inches. Cambridge University Press. New York: Macmillan. 1944. $15.

THIS excellent book was written at a time when the author was much interested in the propagation of electromagnetic waves over the surface of the earth, and consequently one of the important features of the book is that it contains material of interest to the radio engineer. Such a man is interested particularly in the asymptotic expansions of the Bessel functions, in definite integrals involving Bessel functions and in tables of Bessel functions. The subject of asymptotic expansions is treated with the thoroughness characteristic of a master in this field. It may be recalled that in 1912 Watson published in the Rendiconti di Palermo a memoir crowned by the Danish Royal Academy of Science in which among other things he gave expressions for the functions $J_n(x)$, $J_{-n}(x)$, $Y_n(x)$ and $K_n(x)$ as series of inverse factorials.

In Chapter III the Bessel functions of various types are defined for complex values of both the variable and index. The functions of an imaginary variable were required in physical investigations over a hundred years ago, the use of Bessel functions of a complex quantity is almost as old, as it began with work on the motion of a pendulum in a resisting medium. These functions were given a special notation by Lord Kelvin and were much used by electrical engineers

[1] H. A. Edgerton and S. H. Britt, *American Scientist*, 31: 255–262, 1943.
[2] Banesh Hoffman, *American Scientist*, 31: 255, 262, 1943.
[3] H. A. Edgerton and S. H. Britt, *American Scientist*, 31: 263–265, 1943.
[4] Paul F. Brandwein, *Science Education*, 28: 47–49, 1944.
[5] H. A. Edgerton, S. H. Britt and H. M. Davis, *Science Education*, 28: 229, 1944.

interested in the skin effect in the propagation of electric waves of high frequency. The properties of Kelvin's ber and bei functions and their generalizations are given on pages 81–82 and on p. 204, but many special formulae for these functions that are used by engineers are not given explicitly. For these it is necessary to go to the papers of Savidge, Airey, Russell and Whitehead and to the books and papers of Dwight and McLachlan. It may be mentioned in particular that for the numerical calculation of the functions for large values of the variable, Dwight recommends formulae somewhat different from Airey's formulae of p. 204. Tables for these functions are not included, and the author probably did not wish to enter into a lengthy discussion of matters that had been dealt with adequately by other writers.

In Chapter IV there is a useful discussion of the differential equations which can be solved with the aid of Bessel functions. This chapter and the following one contain many series that are often employed in physical investigations.

Chapters VI, XII, XIII and XIV on integral representations and definite integrals provide a mine of information. References to these chapters are given by countless authors of papers in pure and applied science. A valuable feature of these chapters is that the numerous integrals are established by rigorous methods.

The tables at the end of the book are particularly well chosen and form one of the most valuable parts of the book. It may be mentioned, for instance, that a recent formula for the radiative resistance of a cylinder obtained by H. Page, of Manchester University, involved the indefinite integral of the Bessel function $J_0(x)$ for which a table was available in Watson's treatise. In this connection it may be worth while to mention that ten place tables of the integrals of both $J_0(x)$ and $Y_0(x)$ have been published recently by A. N. Lowan and M. Abramowitz.

The expansions of planetary theory, which began with Lagrange's sine series for the difference between the mean and eccentric anomaly, involved Bessel functions of the form $J_{p\pm n}(pe)$ in which the order and argument were both large when p was large. For a discussion of the convergence of these expansions it was necessary to know the behavior of these Bessel functions for large values of p, and the early work of Carlini was followed by that of many other mathematicians. The history of this development is given in Chapter VIII and modern methods of dealing with the problem, such as the method of steepest descent, are clearly explained. The resulting asymptotic expansions are of great importance in physical mathematics, particularly in the theory of the propagation of waves, and Watson has made a notable advance in giving precise conditions under which certain formulae of approximation are applicable. In the most recent work the expressions in terms of the Airy functions are recommended and elaborate tables of these functions have been prepared by a committee of the British Association for the Advancement of Science.

The series of planetary theory are discussed in full in the Chapter XVII on Kapteyn series where a discussion is given of a general type of series which includes those of planetary theory and some series found by Schott and others in researches on the structure of the atom. The book contains also discussions of many other types of series.

The book closes with a very valuable bibliography which is nearly but not quite complete up to 1921. Among the omissions are some papers by Poisson, notably his memoir on the propagation of waves (1816) in which he gave an expression for the inverse distance of two points as an exponential integral involving $J_0(rt)$, and two papers by James Ivory (1832 and 1838) in which Bessel functions of an imaginary argument are used in the problem of astronomical refraction.

In the new edition the only notable change is in the valuable Chapter XV on the zeros of Bessel functions where a reference is made to the work of Siegel (1929) regarding the truth of Bourget's hypothesis that $J_n(z)$, $J_{m+n}(z)$ have no common zero except, perhaps, $z=0$ when m and m are positive integers. Some related theorems have been given by D. Prasad Banerjee in the *Journal of the Indian Mathematical Society* for 1935.

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THE CONTROL OF BILHARZIA

The Control of Bilharzia in Southern Rhodesia. By ALAN MOZLEY. 1944. 307 pp. Southern Rhodesia: Salisbury.

WITH the people of more than one half of the globe subject to the debilitating disease, bilharzia, or schistosomiasis, any discovered method of controlling this serious disease becomes of general interest.

Alan Mozley is a malacologist with wide field experience in both the Old and New Worlds who went out to Southern Rhodesia in the company of Sir Malcolm Watson, director of the Ross Institute of Tropical Hygiene, in order to find out what should be done to control bilharzia as one of the worst diseases of that country.

The aid of a malacologist was invoked since the schistosoma worm that causes the disease passes from the blood vessels of man into water and then into certain snails and thence, after eight or nine weeks,

back into water, where it has to find and enter the skin of man, within a few days, or else perish. In human blood vessels the minute worms mature in some two months and give off their eggs. This parasite has to alternate from snail to man (from the creation onward) or else perish.

The complete destruction of either host would exterminate the parasite! Man prefers to exterminate the snails. That this is feasible was inferred from the facts that these snail hosts are not very numerous nor difficult to locate. There are here only two kinds of water snails that carry the parasite, and each carries but one of the two species of parasites which both live in man, with different preferences, the one infesting the intestines, the other the urinary organs.

Mozley's report is a thoroughly scientific record of three years of strenuous work (1939–42) during which some thousands of different localities were examined and a laboratory established for examination of, and experiments upon, the different snails.

In some localities 90 per cent. of the natives were infected and throughout the country 35 per cent. of natives and 8 per cent. of Europeans suffered from the worser form of the disease. All races of men and all members of society, both poor and well-to-do, were afflicted. Before the advent of civilized man perhaps the disease was held in check by ducks and fish that destroy the snails, but of late the disease is alarmingly increasing, and this seems due to the "White Man's Civilization." For while the snail that causes intestinal bilharzia (*Biomphalaria pfeifferi* (Krs.)) as being the host of *Schistosoma mansoni* may be found in clean, flowing waters, the worser snail (*Physopsis globosa* (Krs.)) as harboring the parasite *Schistosoma haematobium* is to be found in dirty water, contaminated or polluted.

The native habits of drinking from, and of bathing in, all sorts of pools was bad enough, but the European has increased the dangers by careless disposal of wastage and rubbish so that many places abound in trash and dejecta that aid the disease-bearing snails.

Strangely, man's great aid in civilization, the railroad, is strongly to be condemned as favoring the bad snails by giving them shelter through the making of fills, dams, culverts and bridges over waters into which human dejecta are allowed to fall.

The book gives in detail recommendations for coping with all aspects of the bilharzia problem except that left to the physician—the dosing of human patients. When these suggestions shall be carried out the bilharzia of Southern Rhodesia should diminish and not increase, even dwindle to the vanishing point.

Many experiments showed the ease with which the young parasite, called cercaria stage, that leaves the snail can be killed, but either the water is more or less injured or else the materials used are expensive.

The snails themselves are known to be easily killed by some salts of copper, but many of these are expensive. There were also found native plants whose bark, leaves or seed or pods were deadly to snails. Finally a number of good methods were selected for killing the snails without danger to the natives. To solicit the aid of the natives posters are distributed advising them to use these, to them well-known, plants or else "the medicine of the Government," which medicine "kills the snails within two days, but does not hurt a human being." "The Government's doctor has often drunk water into which this medicine has been put, and it has not done" him any harm. This "medicine," containing copper carbonate, is a cheaply obtained mineral, Malachite, which Mozley recommends as one of the most useful means of killing those snails in Southern Rhodesia. Details of its preparation and modes of distribution with many other practical suggestions are given for those who may make use of this most useful work which though needed most by the government of that part of the world has a meaning for all who have to do with the West Indies, Portugal or any part of the world south of these regions, all subject to bilharzia.

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SPECIAL ARTICLES

AN ANTIBIOTIC SUBSTANCE ACTIVE AGAINST MYCOBACTERIUM TUBERCULOSIS

RECENTLY Soltys[1] reported that culture filtrates of a strain of *Aspergillus fumigatus* showed antibiotic activity against *M. tuberculosis*. As far as we know, no isolation of a substance in a pure or even a crude form active against tubercle bacilli has yet been described.

The strain of *A. fumigatus* investigated was isolated in this laboratory as a contamination. Grown at room temperature on Czapek-Dox medium containing 2 per cent. corn syrup, it produced substances active against gram-positive cocci, gram-negative bacilli and some acid-fast bacilli. The test organisms employed were *Staph. aureus* H, a *B. coli* and *M. tuberculosis* BCG17. After 15 to 18 days of growth the medium was, on the average, active against staphylococci in a 1:40 dilution. Activity against *B. coli*

[1] M. A. Soltys, *Nature*, 154: 550, 1944.

[2] A. Vaudremer, *C. R. Soc. Biol.*, 73: 51, 1912; 74: 278 and 752, 1913.

varied independently and was never higher than 1:20. We have reasons to believe that the activity against gram-positive and gram-negative organisms is due to two different substances which might be separated by their selective solubility in organic solvents. The substance active against staphylococci is also active against *M. tuberculosis* BCG. The anti-coli substance is less stable and has not yet been investigated for activity against BCG.

Both substances can be obtained in crude form from the medium, (1) by extraction with chloroform, either directly or after preliminary concentration of the medium; (2) by adsorption onto Norit and subsequent elution with chloroform and (3) by saturation with ammonium sulfate and extraction of the precipitate with chloroform. Chloroform extracts (1) and (3) can be partially decolorized by treatment with Norit with hardly any loss of activity. The active substance seems to be dialysable through Cellophane membranes.

Probably identical substances can also be extracted from the mold itself by alcohol, acetone, chloroform or ether, supporting Vaudremer's[2] observation made with press juice of the same mold.

At present our efforts are directed mainly towards the final purification of the active substance, as the work with crude products has only presumptive value.

The activity of the partially purified preparations was established by the following methods: (1) for staphylococci and *B. coli:* (a) by serial dilutions in papain broth[3]; (b) by a new method, using the permeability of soft agar for testing growth inhibitory substances, the particulars of which will be published separately. (2) For acid-fast organisms by two methods: (a) bacteriostatic action was investigated by making serial dilutions of the substance in Kirchner's[4] medium and inoculating the tubes with a suspension of BCG. Preliminary readings were taken after 5 to 10 days and final examinations for growth were made after 6 weeks; (b) bactericidal action was estimated by incubating a heavy suspension of BCG with different dilutions of the substance for 24 hours and subsequently inoculating Petragnani slants with 0.1 ml of the mixture. Results were read after 6 weeks.

Our experiments with the crude preparations seem to indicate that: (1) they possess a high degree of activity against staphylococci, preventing their growth in 1:700,000 of the dry crude substance; (2) their bacteriostatic activity against BCG appears to be higher, preventing growth in at least 1:1,400,000 dilution; (3) their bactericidal action against BCG is equal to or slightly lower than their anti-staphylococci activity.

[3] I. N. Asheshov, *Can. Publ. Health Jour.*, 32: 468, 1941.

[4] O. Kirchner, *Zbl. f. Bakt.*, I Orig., 124: 403, 1932.

Often a BCG emulsion treated with a 1:500,000 dilution of the active substance produced no growth on Petragnani slants, but occasionally isolated colonies appeared on slants inoculated with lower dilutions. We attribute this phenomenon to imperfect emulsion of the BCG culture, resulting in lumps which protect the bacterial cells from the action of the antibiotic.

No bactericidal action on avian type of *M. tuberculosis* was observed even in dilutions as low as 1:100.

The active substance is poorly soluble in water: the activity of aqueous extracts of the dry substance against staphylococci and BCG never exceeded 1:40,000.

We consider animal experiments on toxicity and activity of the crude substance valueless and are postponing them until preparations of a greater purity are obtained.

The active substance investigated may be similar to fumigacin or helvolic acid (Waksman;[5] Chain *et al.*[6]), though some of its properties seem to indicate that the two antibiotics are not identical.

Some other, as yet unidentified, molds were found to produce active substances against tubercle bacilli and are now under investigation.

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A QUANTITATIVE STUDY OF THE FIBRINOLYSIN-ANTIFIBRINOLYSIN REACTION[1]

THE antifibrinolysin test devised by Tillett and Garner[2] is based upon the observation that Group A hemolytic streptococci produce a substance, fibrinolysin, which dissolves the plasma clot of normal individuals, whereas the plasma clot of individuals convalescent from hemolytic streptococcal infections is generally resistant to lysis. This resistance is attributed to the presence in the blood of specific antibody, antifibrinolysin.

In 1938, Milstone[3] reported that the process of streptococcal fibrinolysis required the presence of an accessory lytic factor normally present in human

[5] S. A. Waksman, SCIENCE, 99: 220, 1944.

[6] E. Chain *et al.*, *Brit. Jour. Exp. Path.*, 24: 108, 1943.

[1] This investigation was supported through the Commission on Acute Respiratory Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of The Surgeon General, United States Army, and by grants from the Commonwealth Fund, the W. K. Kellogg Foundation, the John and Mary R. Markle Foundation and the International Health Division of the Rockefeller Foundation to the Board for the Investigation and Control of Influenza and Other Epidemic Diseases for the Commission on Acute Respiratory Diseases.

[2] W. S. Tillett and R. L. Garner, *Jour. Exp. Med.*, 58: 485, 1933.

[3] H. Milstone, *Jour. Immun.*, 42: 109, 1941.

serum. Studies from this laboratory[4] and those by Christiansen[5] have indicated that, in the fibrinolytic process, the lytic factor is converted by fibrinolysin into an active tryptase. It was shown that the mechanism of streptococcal fibrinolysis consists of two stages:

(1) Activation of the lytic factor by fibrinolysin with the production of an active tryptase.
(2) Dissolution by the tryptase of the fibrin clot.

The present report is concerned with a study of (1) the factors participating in the inhibition of the fibrinolytic reaction, as well as the application of these observations to the formulation of an accurate method for the estimation of serum antifibrinolysin; and (2) observations concerning the relation of specific strains of β-hemolytic streptococci to the antifibrinolysin response in man.

(1) Fibrinolysin-Antifibrinolysin Reaction

Lyophilized preparations of human fibrinogen[6] were kindly supplied by Drs. E. J. Cohn and S. Howard Armstrong, Jr. The fibrinogen contained the lytic factor in adequate and constant amount. The thrombin employed was a highly active commercial preparation (Lederle) from rabbit blood. Fibrinolysin was obtained by alcoholic precipitation according to the procedure of Garner and Tillett.[7]

Observations made on the problem of the resistance of plasma clots to lysis indicated that the inhibition of either one of the two stages of the fibrinolytic mechanism manifested itself as an apparent resistance to the action of fibrinolysin. Thus, the resistance conferred on a fibrin clot by a given serum was found to result from: (a) the presence in the serum of a specific antifibrinolysin; or (b) the presence of antiproteases. Sera having high antiprotease titers measured against preparations of chloroform-activated serum tryptase[8] also yielded high "antifibrinolysin" titers, as might be expected. However, sera possessing elevated antifibrinolysin titers showed no correlation with their antiprotease titers. It was further observed that the resistance to fibrinolysin of sera from cases of pneumococcal pneumonia could be attributed to an elevated antiprotease concentration. In general, the normal sera and the acute and convalescent sera obtained from cases of hemolytic streptococcal infections yielded negligibly low antiprotease titers which did not interfere with the determination of antifibrinolysin.

Antifibrinolysin was found to combine rapidly and specifically with fibrinolysin in multiple proportions depending upon the ratio in which these two substances were mixed. The reaction was thus similar to toxin-antitoxin reactions *in vitro*. The combinations of fibrinolysin and antifibrinolysin was approximately 85 per cent. complete after incubation for thirty minutes at 37° C.

A method was devised for the quantitative determination of antifibrinolysin in serum by the proper control of the concentrations and activities of the reagents participating in the fibrinolytic process. The procedure required the standardization of the three factors: fibrinogen, lytic factor and fibrinolysin. Since the fibrinogen product contained the lytic factor in constant and adequate amount, the use of a single preparation throughout the study simultaneously controlled the fibrinogen and lytic factor concentrations. A solution containing 0.18 per cent. fibrinogen (0.60 g of Fraction I per 100 ml) was employed since it gave a clot which was both firm and readily susceptible to lysis. For standardization, the solution of fibrinolysin was diluted progressively and added in 0.5 ml amounts to a series of tubes containing 0.5 ml of fibrinogen solution and 1.0 ml of buffered saline. The clot was produced by further addition of 0.2 ml of thrombin. Incubation was carried out for 30 minutes at 37° C. The highest dilution permitting complete dissolution of the fibrin clot contained the required concentration of fibrinolysin and this amount was termed one unit.

The procedure for determination of the antifibrinolysin titer of serum was as follows: 0.5 ml amounts (1 unit) of the proper fibrinolysin dilution were added to a series of tubes containing 1.0 ml of sucessive dilutions of serum. After incubation for 30 minutes at 37° C., 0.5 ml of fibrinogen and 0.2 ml of thrombin were added to each tube to form the standard clot. The tubes were then incubated at 37° C. for 60 minutes. The highest dilution of serum which completely prevented lysis of the standard clot after 60 minutes incubation was taken as the titer of the serum. A clot was regarded as lysed if it "ran" or "slid" in the slightest degree when the tube was inverted for ten seconds. The range of serum dilutions employed extended from 1/50 to 1/2,000 (initial dilutions).

This method of determining antifibrinolysin has given reliable and reproducible results. A detailed analysis of the antifibrinolysin titers obtained in a group of 3,504 sera collected from approximately 900

[4] M. H. Kaplan, *Proc. Soc. Exp. Biol. and Med.*, 57: 40, 1944.
[5] L. R. Christiansen, *Jour. Bact.*, 47: 65, 1944.
[6] The product employed was Fraction I of the plasma proteins prepared by the Department of Physical Chemistry, Harvard Medical School, Boston, Massachusetts, from blood collected by the American Red Cross, under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Harvard University.
[7] R. L. Garner and W. S. Tillett, *Jour. Exp. Med.*, 60: 239, 1934.
[8] H. J. Tagnon, C. S. Davidson and F. H. L. Taylor, *Jour. Clin. Invest.*, 21: 525, 1942.

individuals, including normal men as well as those with respiratory diseases, is being presented elsewhere.

(2) Production of Antifibrinolysin

In previous studies,[9] it was demonstrated that bacteriological and clinical evidence of β-hemolytic streptococcal infection is not necessarily sufficient to establish an etiological diagnosis; rather, the development of specific antibody during convalescence is required. In known streptococcal infections, such as scarlet fever and epidemic sore throat, there is a significant increase in antistreptolysin antibodies in about 85 per cent. of the convalescent sera. For the purpose of the present study, patients with exudative tonsillitis or pharyngitis from whom types 3, 5, 19 or 12[10] streptococci were isolated in one or more of three cultures of the throat, and who developed antistreptolysin antibodies during convalescence, are included as *proved* instances of streptococcal infections. In all, 110 hospitalized soldiers are included in this analysis.

The distribution of the cases according to type of streptococcus and the results of the antifibrinolysin determinations are recorded in Table 1. The type 3

TABLE 1

Antifibrinolysin Response in Streptococcal Infections

Type of Group A β-Hemolytic Streptococcus	Occurrence of cases	Antifibrinolysin test		
		No. of cases positive	No. of cases negative	Per cent. positive
3	Endemic	1	9	10
5	Epidemic	15	61	20
19	Endemic	8	5	62
12	Epidemic	10	1	91

and type 19 infections occurred endemically during 1943 and 1944. In contrast, the type 5 infections were the result of a food-borne epidemic, and at least nine of the type 12 infections occurred in a single small outbreak. Presumably, the sporadic cases were produced by several strains of the given types, while the epidemic cases resulted from a single strain.

The variation in the antifibrinolysin response in these subjects was marked. Only one of the type 3 infections exhibited a significant response, whereas a rise in antibodies was demonstrated in 62 per cent. of the type 19 infections. Similarly, there was a difference between type 5 epidemic cases with only 20 per cent. positive antifibrinolysin tests and type 12 infections with 91 per cent. These marked differences in antibody formation suggested that the development of antifibrinolysin in man might be related to the fibrinolytic capacity of the infecting organism.

A test was devised therefore to measure the amount of fibrinolysin produced by these streptococci *in vitro*. The type 12 strains were not available for study. The average production of fibrinolysin of nine of the type 3 strains was found to be 40 units per ml of culture medium, that of the type 5 strains 90 units, and of the type 19 strains 180 units. These results suggest that the antifibrinolysin response in the subjects reported here is related to the ability of the homologous organism to produce fibrinolysin *in vitro*. It should be emphasized, however, that the amount of fibrinolysin produced is not necessarily a property of a given Lancefield type, but may be a strain characteristic. For example, some carrier strains of type 3 streptococci, isolated from the same population groups supplying the above cases, have the ability to produce large amounts of fibrinolysin.

Summary

The results of a study of the streptococcal fibrinolysin reaction and its inhibition by sera containing specific antibody are presented. It was possible to devise a quantitative antifibrinolysin test by controlling the various factors influencing the reaction. In man, the antifibrinolysin response was found to vary according to the strain of streptococcus responsible for the infection.

Commission on Acute Respiratory Diseases[11] in Collaboration with Melvin H. Kaplan

THE IMMUNIZING EFFECT OF CALCIUM PHOSPHATE ADSORBED INFLUENZA VIRUS[1, 2]

For the purpose of enhancing the antigenic activity of certain proteins, toxins and infectious agents a variety of adjuvants have been employed. As applied to influenza virus vaccines, Friedewald[3] has described the adjuvant effect of oily substances and acid-fast bacilli when combined with formalin-inactivated virus. In view of the local reactions resulting from subcutaneous injections of such mixtures in animals, Friede-

[9] Commission on Acute Respiratory Diseases, *Jour. Am. Med. Assn.*, 125: 1163, 1944.

[10] Type specific rabbit serums were made available through the generosity of Drs. Homer T. Swift and Rebecca C. Lancefield.

[11] Members and professional associates of the Commission on Acute Respiratory Diseases are: John H. Dingle, Major, M.C., A.U.S., Director; Theodore J. Abernethy, Major, M.C., A.U.S.; George F. Badger, Captain, M.C., A.U.S.; Joseph W. Beard, M.D.; Norman L. Cressy, Major, M.C., A.U.S.; A. E. Feller, M.D.; Irving Gordon, M.D.; Alexander D. Langmuir, Captain, M.C., A.U.S.; Charles H. Rammelkamp, Jr., M.D.; Elias Strauss, Captain, M.C., A.U.S.; and Hugh Tatlock, 1st Lieutenant, M.C., A.U.S.

[1] From the Department of Epidemiology and the Virus Laboratory, School of Public Health, University of Michigan, Ann Arbor.

[2] These investigations were aided through the Commission on Influenza, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, United States Army.

[3] Wm. F. Friedewald, Science, 99: 453, 1944.

wald has indicated the unlikelihood that the adjuvants he employed could be safely used in humans. Bodily, Corey and Eaton,[4] in a report of experiments with alum-precipitated influenza virus, did not note any adjuvant effect. The purpose of the present report is to record the results of preliminary studies indicating the enhancement and prolongation of the immunizing effect in mice of formalinized influenza virus when absorbed on calcium phosphate[5] and to describe certain other properties of such a preparation.

Allantoic fluid from chick embryos infected with the PR8 strain[6] of influenza virus, Type A, was used as a source of virus. The virus was rendered non-infectious in 48 hours by 0.05 per cent. formalin at 4° C. To each 100 cc of the formalinized fluid was added 1.5 cc of 1 M solution of calcium chloride and 1.5 cc of 1 N solution of sodium hydroxide. (In some fluids the addition of phosphate may be needed to precipitate all the calcium chloride as calcium phosphate at pH 8.0–8.5.) After two washings with 0.05 M phosphate buffer, pH 7.5, the precipitate was resuspended in a volume of the same buffer equal to the volume of the adsorbed fluid. The quantity of virus present in the various fractions was estimated by titrating the hemagglutinating capacity.[7] To do this it was necessary to release the virus absorbed on the calcium phosphate by dissolving the precipitate in citrate solution.[5] The hemagglutinin titers[8] of the formalinized allantoic fluid and the resuspended precipitate of calcium phosphate were 2,560, while the titer of the supernatant fluid after adsorption was 16. Hemagglutinin was not detected in the wash fluids.

The relative immunizing capacities of a single subcutaneous injection of the formalinized allantoic fluid suspension of virus and the calcium phosphate adsorbed virus were tested in mice. Three groups of young adult Swiss mice were selected. The animals in one group were each given 0.5 cc of the allantoic fluid suspension of virus subcutaneously in the region of the upper back; the mice in the second group were similarly treated with the suspension of virus adsorbed on calcium phosphate; a third group was set aside as untreated controls. At intervals of 4, 8 and 14 weeks after vaccination, mice from each of the three groups were tested for immunity to intranasal infection with graded doses of mouse-adapted PR8 virus. The results are shown in Table 1. Serum was obtained, 10 weeks after vaccination, from 5 mice in each group, to determine to what extent serum antibody titers reflected the difference observed in the degree of immunity of the mice inoculated with the respective preparations. It was of interest that the antibody titers,[8] as measured by the agglutinin-inhibition reaction,[7] were 256 and 512, in the animals vaccinated with free and adsorbed virus, respectively.

TABLE 1

IMMUNITY IN MICE FOLLOWING SUBCUTANEOUS INOCULATION OF CALCIUM PHOSPHATE—ADSORBED AND UNADSORBED FORMALINIZED INFLUENZA, TYPE A (PR8)

Interval between vaccination and infection	Vaccine	Intranasal test dose: *Virus dilutions* 10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-7}
4 weeks	Adsorbed	0,0,0,0,0,0	0,0,0,0,0,0	0,0,0,0,0,0	.....	.....	.....	.....
	Unadsorbed	4,6,7,8, ++++,++	4,5,++,+,± ,0	+,+,+,0,0,0	.....	.....	.....	.....
	Controls	.....	.....	.....	.....	5,5,5,5,6, ++++	6,6,7,8,10,+	10,++++,++, ++,++,0
8 weeks	Adsorbed	0,0,0,0,0,0	0,0,0,0,0,0	0,0,0,0,0,0	0,0,0,0,0,0	.....	.....	.....
	Unadsorbed	4,4,5,5,5,+	5,5,++,+,+,±	5,5,7,++,++,+	6,+++,++,+, ±,0	.....	.....	.....
	Controls	.....	.....	.....	.....	5,6,6,7,7,7	9,++++,+++, ++,+,±	+++,+++,0, 0,0,0
14 weeks	Adsorbed	+,+,+,0,0,0	0,0,0,0,0,0	0,0,0,0,0,0	0,0,0,0,0,0	.....	.....	.....
	Unadsorbed	.....	6,6,6,7,8,8	6,6,6,+++,+,+	+++,+++,++ +,±,0	+++,++,++, 0,0,0	.....	.....
	Controls	.....	.....	.....	4,5,5,5,6,6	4,5,5,6,6, ++++	9,++++,++++, +++,++,+	+++,+++,+, +,+,0

Numerals denote day of death of individual mice.
Symbols 0 to ++++ indicate degree of pulmonary involvement in survivors autopsied on 10th day after infection.

The sites of inoculation were examined for indications of inflammatory reaction; none were seen externally. On dissection, the precipitate of calcium phosphate was found freely movable in the subcutaneous tissue, without gross evidence of inflammation. Histological examination revealed a typical foreign-body reaction with marked reticulo-endothelial response. The deposit diminished in size in the course of four months, but had not disappeared at the end of this interval.

No untoward reactions were observed in 5 human

[4] H. L. Bodily, M. Corey and M. D. Eaton, *Proc. Soc. Exp. Biol. and Med.*, 52: 165, 1943.
[5] J. E. Salk, *Proc. Soc. Exp. Biol. and Med.*, 46: 709, 1941.
[6] T. Francis, Jr., SCIENCE, 80: 457, 1934.
[7] G. K. Hirst, SCIENCE, 73: 335, 1941.
[8] J. E. Salk, *Jour. Immunol.*, 49: 87, 19[illegible]

subjects who were given a 1 cc injection, subcutaneously, of the calcium phosphate-virus suspension containing the virus adsorbed from 1 cc of formalinized allantoic fluid containing Type A virus and 1 cc of fluid containing Type B virus. The sites of inoculation were examined over a period of 18 days. The reactions observed were similar to those seen in 5 other subjects who had received a corresponding dose of allantoic fluid suspension of both viruses. The sharp stinging pain that followed the injection of the formalinized allantoic fluid did not occur after the injection of the adsorbed material which was free of formaldehyde.

The stability of the hemagglutinating capacity of the formalin-inactivated virus adsorbed on calcium phosphate and of the original formalinized allantoic fluid suspension of virus, stored at 4° C., room-temperature and 37° C., has been tested over a period of 4 months. The results are shown in Table 2. Whether

TABLE 2

STABILITY OF HEMAGGLUTINATING CAPACITY OF CALCIUM PHOSPHATE—ADSORBED AND UNADSORBED FORMALINIZED INFLUENZA VIRUS, TYPE A (PR8), AFTER STORAGE FOR 4 MONTHS AT DIFFERENT TEMPERATURES

Temperature	Preparations	Final dilutions								
		40	80	160	320	640	1280	2560	10,240 5120	
4° C.	*Adsorbed	+	+	+	+	+	+	+	±	0
	*Unadsorbed	+	+	+	+	+	+	±	0	
Room temperature	Adsorbed	+	+	+	+	+	+	±	0	
	Unadsorbed	+	+	±	0	0	0	0	0	
37° C.	Adsorbed	+	+	+	+	+	+	0	0	0
	Unadsorbed	0	0	0	0	0	0	0	0	

* Titers after 4 months at 4° C. were the same as at the start of the experiment.
Symbols: + = complete agglutination;
± = partial or slight agglutination;
0 = no agglutination.

the greater stability of the adsorbed-virus is due to removal from prolonged contact with formaldehyde or to some protective effect of adsorption will be determined.

Further studies are in progress to determine the mechanism of the adjuvant effect and the quantitative relationship between dosage and antigenic activity of free and adsorbed virus as measured by antibody response and immunity to infection. A more detailed report of these studies in other hosts as well as mice will be made.

JONAS E. SALK

PROLONGATION OF PENICILLIN ACTIVITY BY MEANS OF ADRENALIN[1]

THE rapid absorption and excretion of penicillin following its injection by various routes is well known, and interest has been shown in methods to prolong effective blood concentration levels of this antibiotic. Thus the use of penicillin in beeswax-peanut oil mixtures[2] and the application of ice bag chilling at the site of injection[3] have been reported as procedures which prolong penicillin absorption. It occurred to

AVERAGE BLOOD CONCENTRATION LEVELS OBTAINED IN RABBITS FOLLOWING THE INJECTION OF AQUEOUS AND ADRENALIN SOLUTIONS OF CALCIUM PENICILLIN

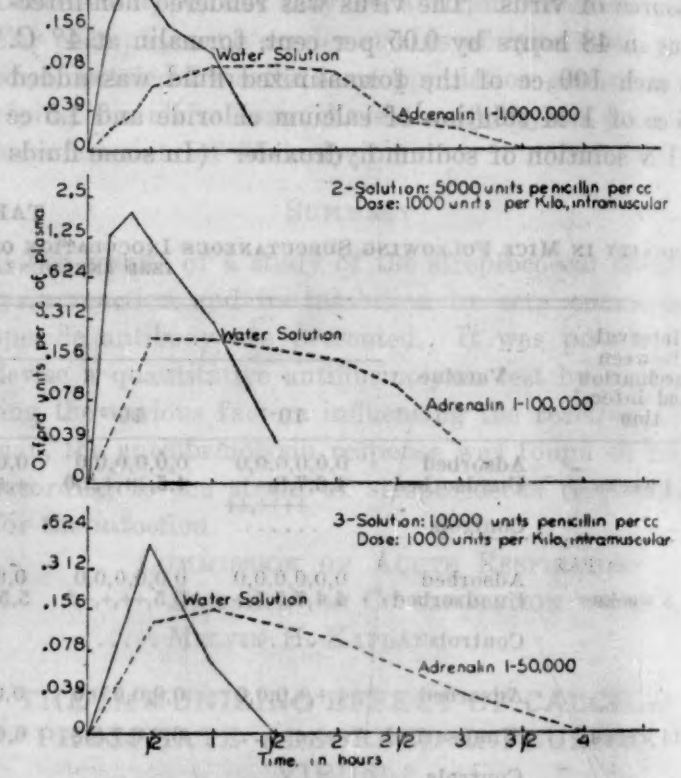

FIG. 1. (1) Each curve represents an average of values obtained from 10 determinations made on 5 rabbits. (2) Each curve represents an average of values obtained from 3 determinations made on 3 rabbits. (3) Each curve represents an average of values obtained from 5 determinations made on 5 rabbits.

the authors that adrenalin, because of its vasoconstricting properties, might afford a practical method for accomplishing this effect. The behavior of adrenalin is well established and the injection of this substance is not attended by the objectionable local tissue reactions[4] sometimes resulting from the use of vehicles such as vegetable oils which are being employed to hinder the absorption of certain therapeutic agents.

Tests were run by *in vitro* methods to determine

[1] From the Collis P. and Howard Huntington Memorial Hospital, Pasadena, and the Departments of Bacteriology and Pathology, School of Medicine, University of Southern California, Los Angeles, California. Valuable technical assistance was provided by Patrice Morrow.

[2] M. J. Romansky and G. E. Rittman, SCIENCE, 100: 196–198, 1944.

[3] M. Trumper and A. M. Hutter, SCIENCE, 100: 432–434, 1944.

[4] R. C. Page and E. J. DeBeer, *Am. Jour. Med. Sciences*, 205: 812–814, 1943.

the stability of penicillin in adrenalin solutions at different temperatures and animal experiments were carried out to learn the effect of adrenalin on the rate of penicillin absorption as measured by blood level concentrations obtained following subcutaneous or intramuscular injections.

Calcium penicillin which assayed at 500 Oxford units per mg and which was prepared from surface fermentation cultures of *Penicillium notatum* was used in all animal experiments. Solutions containing 500 units of calcium penicillin per cc and adrenalin in concentrations not exceeding 1–16,000 showed no loss of activity, compared with aqueous control solutions, when kept for 24 hours at 37° C, 5° C or at room temperature. The assays for penicillin stability were run by the cylinder plate method using *Bacillus subtilis* as the test organism.

Animal experiments were run with rabbits which were injected alternately with experimental preparations and aqueous control solutions. Injections were made subcutaneously or intramuscularly and blood samples collected from the ear veins. Penicillin assays were run on plasma by the broth dilution method of titration using a culture of *Streptococcus pyogenes* as the test organism.

The injection of aqueous solutions of penicillin resulted in blood level concentrations which showed maximum bacteriostasis after about 20 minutes with little or no activity remaining in plasma collected after 1 or 1½ hours. The addition of adrenalin to penicillin solutions produced a significant change in the blood level concentrations obtained in all experiments. As may be seen in Fig. 1, the effect of adrenalin was to flatten the blood activity curves so that compared with control tests, lesser concentrations of penicillin were found in early bleedings and a prolongation of activity was observed in samples collected from 1½ to 3 hours after injection. This occurred when the material was administered by either the subcutaneous or the intramuscular method. Small amounts of adrenalin added to aqueous solutions of penicillin usually doubled the time during which a bacteriostatic concentration could be detected in blood samples.

The outcome of these experiments suggested the clinical use of adrenalin in penicillin therapy and preliminary trials indicate that humans may be expected to respond in a manner similar to the experimental animals employed. The effect of adrenalin was tested in 7 subjects[5] injected by the intramuscular route with freshly prepared solutions of 50,000 units of sodium penicillin dissolved in 4 cc of 1–50,000 adrenalin and in 2 patients who received 20,000 units contained in 2 cc of 1–25,000 adrenalin. Six control subjects were injected by the same method with saline solutions of penicillin and blood level titrations were run by a method similar to that of Rammelkamp.[6] The prolongation of bacteriostatic serum levels produced by adrenalin, which may be seen from the results summarized in Table 1, was sufficiently great to indicate further investigation with this vasoconstrictor. Until the most efficient adrenalin and penicillin mixtures can be worked out, it would appear from observations made in the present study that the use of small amounts of adrenalin in conjunction with penicillin may find immediate application in the usual method of administering this antibiotic by repeated intramuscular injections.

TABLE 1

BLOOD LEVEL CONCENTRATIONS OF PENICILLIN FOLLOWING THE INTRAMUSCULAR INJECTION OF ADRENALIN SOLUTIONS IN HUMAN SUBJECTS

Subject	Treatment	Hours after injection							
		½	1	1½	2	2½	3	3½	4
1	50,000 units sodium penicillin in 4 cc of saline	.624		.039		0		0	
2		.312		.039		0		0	
3		.624	.624		.078		0		0
4		1.25	.624		.039	0	0		0
5		1.25	.624		.039	0	0		0
6	50,000 units sodium penicillin in 4 cc of saline plus .08 cc of 1–1000 adrenalin	.156		.156		.039		0	
7		.624		.312		.039		0	
8			.624		.156		0		0
9		.312	.624		.624		.312		
10		1.25		.312		.078		0	
11		.624	.624		.156	.039	0		0
12		.312	.624		.156	.039	.039		0
13	20,000 units, 2 cc saline	.624	.156		0		0		0
14	20,000 units as above plus .08 cc of 1–1000 adrenalin	.039	.078		.039		0		0
15		.078	.078	.039	.039	.015	0		

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GORDON ALLES

[5] The penicillin blood concentration studies on human subjects were made possible through the generous cooperation of Doctors Herbert Cowper and Harold Mazur of the Los Angeles City Health Department and Mr. Charles Arthur of the Pasadena City Health Department.

[6] C. H. Rammelkamp, *Proc. Soc. Exp. Biol. and Med.*, 51: 95–97, 1942.

SCIENTIFIC APPARATUS AND LABORATORY METHODS

A CHIN-OPERATED FOCUS ADJUSTMENT FOR THE DISSECTING MICROSCOPE

WHEN performing an operation under a standard dissecting microscope, it is necessary to use the hand adjustment in order to bring the instrument into focus at a new level. The frequency with which these adjustments must be made when working at a high magnification is sometimes very annoying. Furthermore, when both hands are required for the manipulation of the object it becomes necessary to interrupt the operation each time the focus of the instrument must be corrected and this may seriously affect the quality of the work.

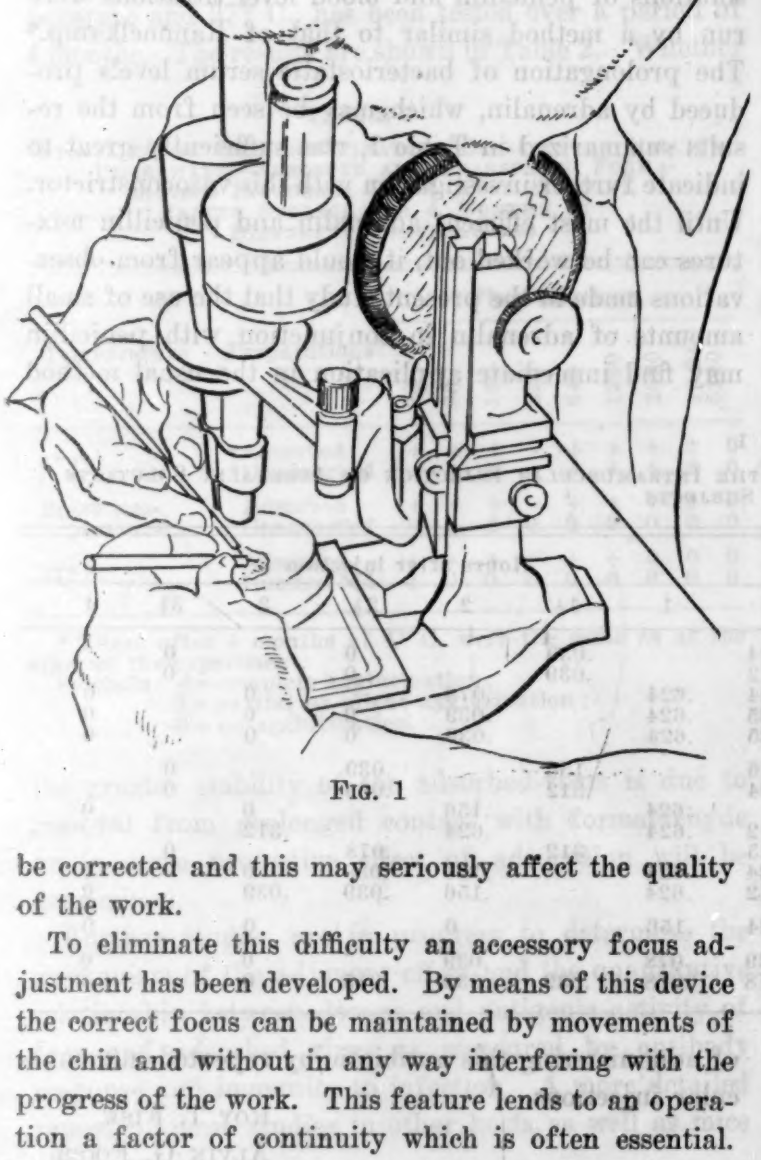

FIG. 1

To eliminate this difficulty an accessory focus adjustment has been developed. By means of this device the correct focus can be maintained by movements of the chin and without in any way interfering with the progress of the work. This feature lends to an operation a factor of continuity which is often essential. The convenience with which the operative field can be kept in focus encourages a more critical observation and helps to conserve time, effort and patience.

The accompanying figures show how chin-operated focus adjustments have been designed for microscopes of two different models.

Fig. 1 shows a most satisfactory arrangement for a microscope which has its body supported by a jointed arm and swivel. The body of the microscope is simply shifted laterally to a position in front of one of the hand-adjustment controls. A wooden disc of appropriate diameter (about 9 centimeters) is then attached to the corresponding control and serves to transmit the movements of the chin to the mechanism.

Fig. 2 shows a chin-operated adjustment adapted to a microscope of a model more commonly used. The

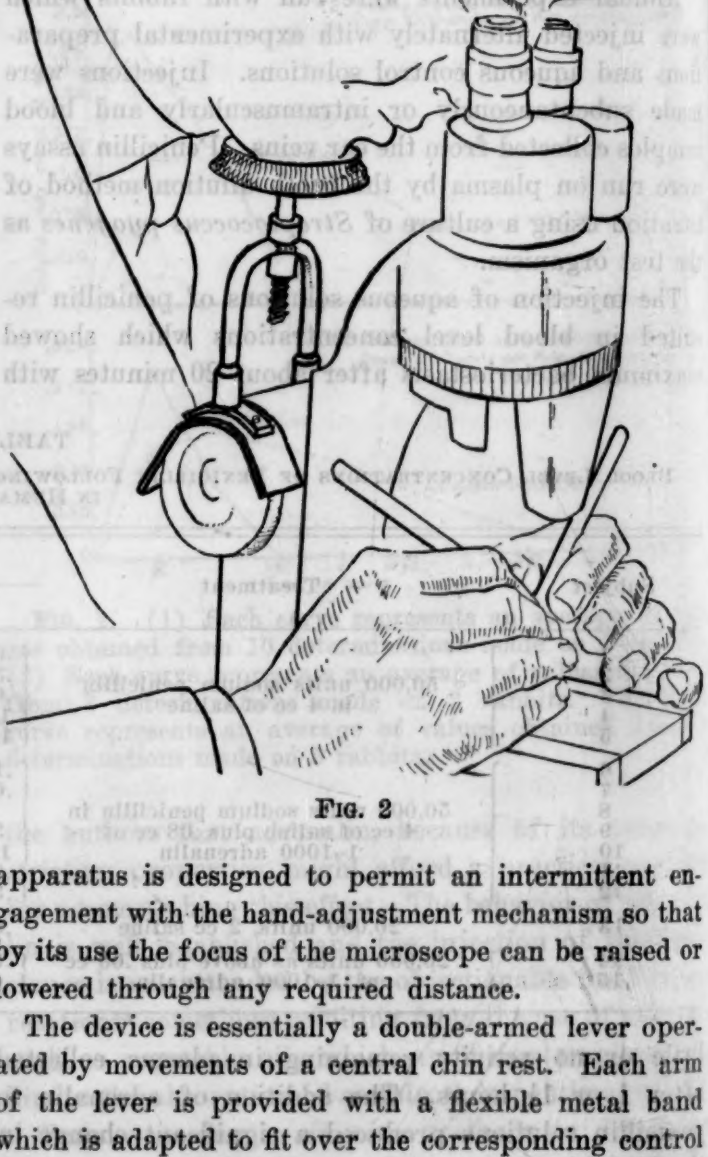

FIG. 2

apparatus is designed to permit an intermittent engagement with the hand-adjustment mechanism so that by its use the focus of the microscope can be raised or lowered through any required distance.

The device is essentially a double-armed lever operated by movements of a central chin rest. Each arm of the lever is provided with a flexible metal band which is adapted to fit over the corresponding control of the hand adjustment, as is shown from a lateral view in Fig. 3. Each band is reinforced in the region of its attachment to the lever arm by an additional strip of metal and is lined with a friction-producing material over a corresponding extent of its inner curvature. On either side of the reinforced portion the

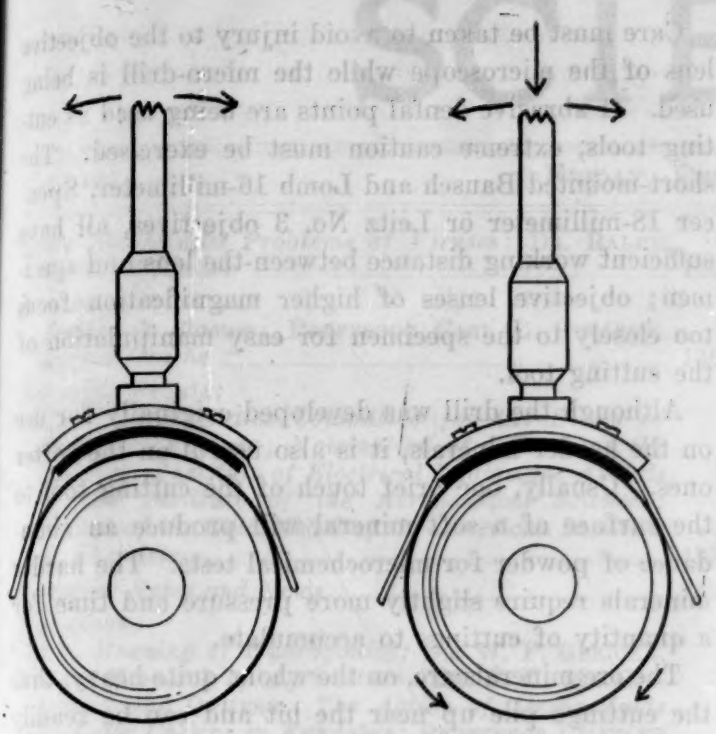

FIG. 3

band retains its flexibility and is tangent to the hand-adjustment control upon which it rests (Fig. 3, left). When the apparatus is in this position the friction between it and the hand adjustment is not sufficient to cause an active engagement, provided the tension on the pinion of the hand adjustment is properly regulated.

The apparatus is brought into use by first exerting a slight downward pressure on the chin rest. The lining of each band is thus brought into effective contact with the hand adjustment mechanism. The focus is then corrected by a second movement of the chin in the proper direction (Fig. 3, right). By a succession of such movements the focus of the microscope can be raised or lowered rapidly through any required amplitude. When not in use the lever may either be pushed forward to rest against the body of the microscope or lifted off the instrument.

For assembling the apparatus illustrated two lens holders of a brass construction furnished the greater part of the material. Their handles were soldered together end to end and bent to form an arched lever arm spanning the hand-adjustment controls. An ordinary rubber furniture coaster was then mounted on a metal plate and attached to this arm by means of an adjustable screw (Fig. 2). The flexible metal band forming the body or lens receptacle of each holder was adapted to fit over the hand adjustment in the manner described (Fig. 3).

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AN EXPERIMENTAL MICRO-DRILL

A PERFECTED technique of working on polished surfaces under the microscope is acquired only with practice, but even the experienced worker often has difficulty in scratching, or obtaining material for a microchemical test from some of the harder minerals such as arsenopyrite (hardness 5.5–6) or others in the group listed as hard minerals by Short.[1]

During the past two years of work with polished surfaces, the writer has been experimenting with a small, electrically powered drill for use on polished surfaces. Some practice is necessary to become a skilful operator of the instrument, but in the writer's opinion, the results obtained are well worth the time spent in developing the proper technique.

When a particularly small area of hard mineral surface is under observation, a sewing needle ordinarily is used as a scoring medium. However, a needle strong enough to score the mineral without breaking usually is so large that it is cumbersome and can not be readily controlled. The problem of obtaining a portion of the hard mineral for microchemical purposes can be overcome by use of the micro-drill which is herein described.

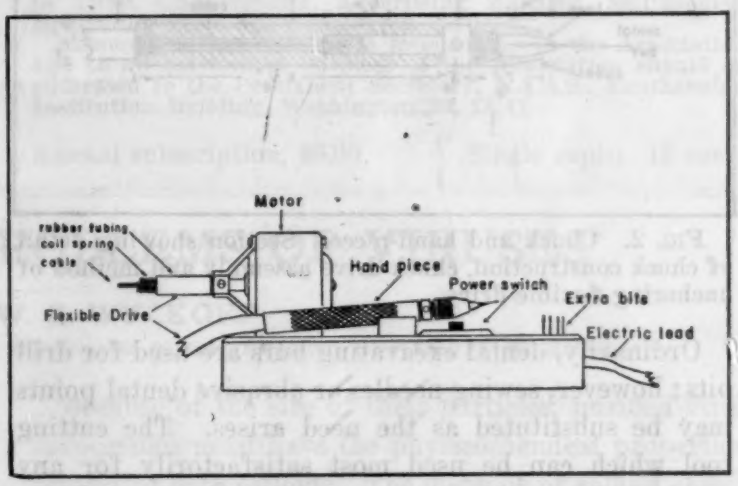

FIG. 1. Micro-drill. The flexible drive assembly interrupted to show construction.

The micro-drill (Fig. 1) consists of a motor mounted on a wooden base $9\frac{1}{2}'' \times 5\frac{1}{2}'' \times 1\frac{1}{2}''$, a flexible shaft connected to the motor at one end and to a handpiece and chuck-drive arrangement at the other, and a chuck to hold the cutting tool. The base also contains the power switch, clamp for the drill and space for a variety of drill bits.

The motor is small, similar to the type used on electric fans. It is manufactured by the F. H. Smith Mfg. Co., New York City, and is rated at 40 watts with speed of 3,400 r.p.m.

[1] N. M. Short, "Microchemical Determination of the Ore Minerals," *U.S.G.S. Bulletin* 914, 2nd ed., pp. 110–111, 1940.

As the instrument is small, some difficulty was experienced in obtaining a lightweight, flexible shaft. After a number of unsuccessful attempts, a suitable shaft was constructed and is described as follows: The shaft-housing is a 24″ length of nickel-plated, curtain rod, coil-spring having an outside diameter of 3/16″ and an inside diameter of ⅛″. One fourth inch rubber tubing forms the outer covering of the drive assembly. The cable, or actual driving part of the shaft, was obtained by unwinding the two outer layers of the flexible cable-drive of a discarded hair clipper. A 3/32″ cable which fitted freely into the housing thus was obtained. One end of the assembled drive was then anchored to the motor shaft by brass fittings, while the other end was fitted into a hand-piece and drive attachment for the chuck.

The chuck (Fig. 2) is a split jaw type and screws onto the drive fittings at the free end of the flexible shaft. By changing the jaws of the chuck, either needles or dental burs may be used.

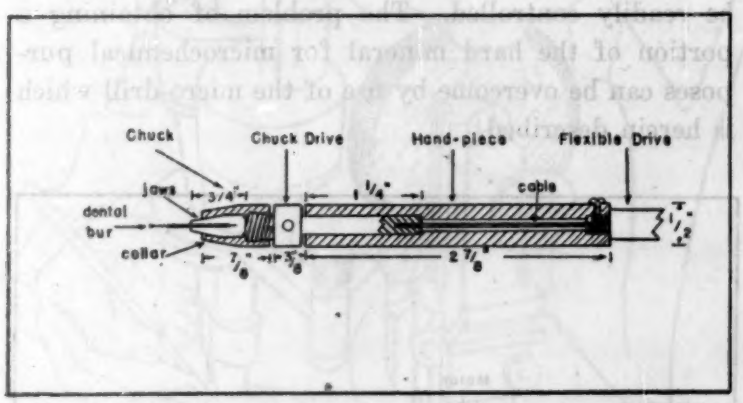

FIG. 2. Chuck and hand-piece. Section showing detail of chuck construction, chuck drive assembly and method of anchoring flexible drive.

Ordinarily, dental excavating burs are used for drill bits; however, sewing needles or abrasive dental points may be substituted as the need arises. The cutting tool which can be used most satisfactorily for any given test is dependent not only on the size and hardness of the mineral particle but also on the skill of the operator. The smallest standard dental bur is 800 microns or 0.8 millimeter in diameter, and as the cutting heads of the burs are spherical, the smallest, serviceable cutting area is 50–70 microns. Unless extremely small areas are being studied, standard excavating dental burs make the most efficient cutting tool. For very hard metallic minerals or hard gangue minerals, abrasive dental points may be required. The smallest, standard abrasive points are from 2–3 millimeters in diameter and must be dressed or worked down to usable size. The dental burs and abrasive points used were manufactured by the S. S. White Dental Mfg. Co., Philadelphia, Pa., and are listed in their general catalogue for 1943 on pages 63, 64 and 66.

Care must be taken to avoid injury to the objective lens of the microscope while the micro-drill is being used. If abrasive dental points are being used as cutting tools, extreme caution must be exercised. The short-mounted Bausch and Lomb 16-millimeter, Spencer 18-millimeter or Leitz No. 3 objectives, all have sufficient working distance between the lens and specimen; objective lenses of higher magnification focus too closely to the specimen for easy manipulation of the cutting tool.

Although the drill was developed originally for use on the harder minerals, it is also useful on the softer ones. Usually, one brief touch of the cutting tool to the surface of a soft mineral will produce an abundance of powder for microchemical tests. The harder minerals require slightly more pressure and time for a quantity of cuttings to accumulate.

The ore minerals are, on the whole, quite heavy, thus the cuttings pile up near the bit and can be readily collected and transferred to a glass slide. The transfer may be accomplished by the method recommended by Short[2] or they may be brushed from the specimen onto the glass slide with a small, soft brush.

The instrument, with suitable points, can be used for the index-marking of thin sections, hand specimens or metal objects.

The experimental micro-drill works well, but the present design has some minor defects. The writer, in cooperation with Mr. Roy Kayler, Machine Shop Foreman, General Maintenance Shops of the University of Idaho, is working on an improved design. The new model will have ball-bearing joints and a smaller and improved chuck.

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[2] N. M. Short, *U.S.G.S. Bulletin* No. 914, 2nd ed., pp. 176–177, 1940.

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